Cancer Treatment and Research
Series Editor: Steven T. Rosen

Gerald Soff *Editor*

Thrombosis and Hemostasis in Cancer

Indexed in
PubMed/Medline

Springer

Cancer Treatment and Research

Volume 179

Series Editor

Steven T. Rosen, Duarte, CA, USA

This book series provides detailed updates on the state of the art in the treatment of different forms of cancer and also covers a wide spectrum of topics of current research interest. Clinicians will benefit from expert analysis of both standard treatment options and the latest therapeutic innovations and from provision of clear guidance on the management of clinical challenges in daily practice. The research-oriented volumes focus on aspects ranging from advances in basic science through to new treatment tools and evaluation of treatment safety and efficacy. Each volume is edited and authored by leading authorities in the topic under consideration. In providing cutting-edge information on cancer treatment and research, the series will appeal to a wide and interdisciplinary readership. The series is listed in PubMed/Index Medicus.

More information about this series at http://www.springer.com/series/5808

Gerald Soff
Editor

Thrombosis and Hemostasis in Cancer

Springer

Editor
Gerald Soff
Medicine/Hematology
Memorial Sloan Kettering Cancer Center
New York, NY, USA

ISSN 0927-3042 ISSN 2509-8497 (electronic)
Cancer Treatment and Research
ISBN 978-3-030-20314-6 ISBN 978-3-030-20315-3 (eBook)
https://doi.org/10.1007/978-3-030-20315-3

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To Jack Levin MD, Uri Seligsohn MD, and Robert D. Rosenberg MD, Ph.D. The three great mentors during my training.

To my family, Laurie, Benjamin, Aaron, and Sam. The Lord blessed me with such a great wife and sons.

To Ola C. Landgren, MD, Ph.D., and Sergio A. Giralt, MD, FACP, world leaders in multiple myeloma and transplant, to whom I owe my life.

To my many fantastic colleagues at Memorial Sloan Kettering Cancer Center: physicians, fellows, house officers, physician assistants, nurse practitioners, nurses, technicians, administrators, housekeepers, food service staff, transportation staff, and volunteers (I hope I did not forget anyone!). All devoted to the mission of helping patients and their families during their battle against cancer.

Preface

I arrived at Memorial Sloan Kettering Cancer Center, in 2009, to establish a Benign Hematology Service. At that time, there had been no faculty members devoted to the hematologic issues in cancer.

Having spent the prior 20 years studying the complex interface of the coagulation system and cancer, I appreciated the many unmet needs and opportunities. As the well-known expression says, "I was like a kid in a candy store." There were so many exciting and interesting questions to tackle! Dr. George Bosl, Chairman of the Department of Medicine at the time, gave me guidance which has served me and many others well. *Our mission is not simply to provide the best cancer care anywhere. Our mission is to change the way cancer is treated*. I took this to heart.

But first, I had to deal with reality of the task in front of me. I had a lot to learn. Shortly after I arrived, I received an emergent call from the Urgent Care Center to see a young patient with metastatic germ cell cancer, who was found to have a saddle pulmonary embolism. I was expecting to find him in extreme distress, possibly requiring resuscitation. However, when I arrived, he was sitting up comfortably in his bed, completely asymptomatic, and surprised at all the commotion. My vital signs were less stable than his. I had not yet become familiar with the large number of asymptomatic or "incidental" pulmonary emboli that are picked up every day in cancer patients, through routine radiographic imaging.

With time, I learned to appreciate the important differences between thrombosis and hemostasis in the setting of cancer from the general population. Cancer and cancer-related treatment represent an added level of complexity to the diagnosis and management of thrombosis and other abnormalities of hemostasis. As one of many examples, the D-dimer is routinely elevated from cancer itself, so this biomarker has limited utility to rule out venous thromboembolism. As a second example, both thrombosis and thrombocytopenia are common in cancer patients. How does one manage the need for therapeutic anticoagulation in the setting of chemotherapy-induced thrombocytopenia? These topics, and many others, are addressed in this text.

The authors of the 13 chapters within this text are all academic specialists, who spend most of our efforts in the field of thrombosis and hemostasis in cancer. Our goal in writing this text is to provide a thorough and practical resource to help the practitioner understand and manage the wide range of thrombosis and hemostasis challenges within their cancer patient population. Of course, we also hope this text

will serve as a valuable resource for trainees, other specialists, and advanced practice providers. Most importantly, we hope that this resource will help cancer patients.

New York, USA Gerald Soff

Contents

Contributors

M. D. Alfred Ian Lee Department of Internal Medicine, Yale School of Medicine, New Haven, CT, USA

Marc Carrier Department of Medicine, Ottawa Hospital Research Institute, General Campus, University of Ottawa, Ottawa, ON, Canada

M. D. Debbie Jiang Department of Internal Medicine, Yale School of Medicine, New Haven, CT, USA

Anna Falanga Department of Transfusion Medicine and Hematology, Hospital Papa Giovanni XXIII, Bergamo, Italy;
School of Medicine and Surgery, University of Milan Bicocca, Monza, Italy

Aime T. Franco Department of Physiology and Biophysics, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Alok A. Khorana Taussig Cancer Institute Cleveland Clinic, Cleveland, OH, USA

Grégoire Le Gal Department of Medicine, Ottawa Hospital Research Institute at the University of Ottawa, Ottawa, ON, Canada

Anjlee Mahajan Division of Hematology and Oncology, UC Davis School of Medicine, UC Davis Cancer Center, Sacramento, CA, USA

Simon Mantha Department of Medicine, Hematology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Charlene Mantia Division of Hematology and Oncology, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, USA

Jodi V. Mones Hematology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Anita Rajasekhar Division of Hematology/Oncology, Department of Medicine, University of Florida, Gainesville, FL, USA

Raajit K. Rampal Department of Medicine, Leukemia Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Joanna Roopkumar Taussig Cancer Institute Cleveland Clinic, Cleveland, OH, USA

Laura Russo Department of Transfusion Medicine and Hematology, Hospital Papa Giovanni XXIII, Bergamo, Italy

Kamya Sankar Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Francesca Schieppati Department of Transfusion Medicine and Hematology, Hospital Papa Giovanni XXIII, Bergamo, Italy

Marie Scully University College London Hospitals, London, UK

Gerald Soff Hematology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Brady L. Stein Division of Hematology and Oncology/Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA;
Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA

Michael B. Streiff Division of Hematology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Mari R. Thomas University College London Hospitals, London, UK

Jerry Ware Department of Physiology and Biophysics, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Ted Wun Division of Hematology and Oncology, UC Davis School of Medicine, UC Davis Clinical and Translational Sciences Center (CTSC), Sacramento, CA, USA

Jeffrey I. Zwicker Division of Hemostasis and Thrombosis, Division of Hematology and Oncology, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA, USA

Abbreviations

APL	Acute promyelocytic leukemia
ATRA	All-trans retinoic acid
bFGF	Basic fibroblast growth factor
CAT	Cancer-associated thrombosis
CLEC-2	C-type lectin receptor type-2
CP	Cancer procoagulant
CRP	C-reactive protein
CVADs	Central venous access devices
DIC	Disseminated intravascular coagulation
DOACs	Direct oral anticoagulants
ECM	Extracellular matrix
ET	Essential thrombocythemia
G-CSF	Granulocyte colony-stimulating growth factor
HS	Heparan sulfate
IMiDs	Immunomodulatory imide drugs
LMWH	Low molecular weight heparin
LPS	Lipopolysaccharides
miRNA	MicroRNA
MPs	Microparticles
MPNs	Myeloproliferative neoplasms
MPO	Myeloperoxidase
NETs	Neutrophil extracellular traps
NK cells	Natural killer cells
PAI-1	Plasminogen activator inhibitor-1
PAI-2	Plasminogen activator inhibitor-2
PMP	Platelet-derived MP
PS	Phosphatidylserine
sP-selectin	Soluble P-selectin
TF	Tissue factor
TF-MP	Tissue factor-expressing microparticles
TFPI	Tissue factor pathway inhibitor
TM	Thrombomodulin
TMA	Thrombotic microangiopathy

tPA	Tissue-type plasminogen activator
uPA	Urokinase-type plasminogen activator
VEGF	Vascular endothelial growth factor
VKAs	Vitamin K antagonists
VTE	Venous thromboembolism
vWF	von Willebrand factor

Thrombosis and Hemostasis in Cancer. Scope of the Problem and Overview

1

Gerald Soff

Contents

"The frequent concurrence of phlegmasia alba dolens with an appreciable cancerous tumor, led me to the inquiry whether a relationship of cause and effect did not exist between the two, and whether the phlegmasia was not the consequence of the cancerous cachexia" (translated from the original French). This famous quote, delivered in a lecture by Armand Trousseau in 1865, is widely recognized as the initial and insightful understanding of the relationship of thrombosis and cancer [1]. There is some debate if an initial description was published even earlier, in 1823, by Bouillaud [2]. But there is no doubt that this association has been widely recognized and accepted for over 150 years. The thrombotic tendency observed in cancer patients is the earliest recognition of a paraneoplastic syndrome, and one that remains a major cause of morbidity and mortality in cancer patients [3].

While the association of thrombosis with cancer has been recognized for over 150 years, it is only in the past 10–15 years that we have made the most dramatic changes in understandings of the pathophysiology of thrombosis in cancer and improved therapy. New laboratory tools have helped clarify the inherent association of activation of the coagulation system by cancer and the biological behavior of

G. Soff (✉)
Memorial Sloan-Kettering Cancer Center, 1275 York Ave, Howard-717, New York, NY 10065, USA
e-mail: Soffg@mskcc.org

G. Soff (ed.), *Thrombosis and Hemostasis in Cancer*, Cancer Treatment and Research 179, https://doi.org/10.1007/978-3-030-20315-3_1

aggressive tumors. New treatment options have led to improvements in management of patients with cancer-associated thrombosis (CAT). In the following chapters, experts in the field of thrombosis and hemostasis in cancer present the current understanding of a wide range of topics related to this association.

In Chap. 2, the complex pathophysiology of the thrombotic tendency in cancer is discussed. Circulating microparticles (MP), derived from platelets and cancer cells, express tissue factor (TF), and phosphatidylserine (PS) on their surface, leading to a potent procoagulant effect throughout the circulation [4, 5]. In Chap. 2, Anna Falanga, Francesca Schieppati, and Laura Russo present the growing complexity of the interaction of the coagulation system and cancer, including the mechanisms by which cancers enhance the prothrombotic state. This includes enhanced expression of a range of coagulation factors, including Factors VII and VIII, and changes to the fibrinolytic pathway. They also note the strong interaction of cancer cells and platelets, leukocytes, and endothelial cells, which results in the expression of a procoagulant phenotype. Beyond simply promoting thrombosis, the changes in the coagulation profile induced by aggressive cancers also impact the biology of the cancer itself, including enhancement of angiogenesis and the metastatic potential. As the understanding of the genetic basis of cancer has advanced, the relationship of the altered genomic profile in cancer with the altered coagulation balance is becoming clarified. This is shown in Fig. 6 of Chap. 2.

In Chap. 3, Aime T. Franco and Jerry Ware continue the discussion of pathophysiology, focusing on the role of platelets in cancer biology. The link between platelet number and function and cancer biology was first recognized by Gasic and colleagues in 1968, who recognized that thrombocytopenia and antiplatelet drugs can reduce metastases in murine models of human cancers [6, 7]. In an epidemiologic study of a large clinical dataset, use of aspirin, with or without Clopidogrel, was associated with a significantly reduced incidence of cancer [8]. In this chapter, Franco and Ware provide current understanding of the complex interaction of platelets, cancer biology, and cancer-associated thrombosis. These processes include induction of angiogenesis and facilitation of metastasis.

Intriguing, recent studies have even suggested that platelets may affect genomic expression in malignant cells, by transfer of microRNAs (miRNAs) [9]. Further different miRNAs from platelet microparticles have been shown to influence cancer growth through multiple mechanisms. These include modulation of immune surveillance, suppressing natural killer cell activation, or increasing phagocytic phenotype of macrophages [10, 11], and facilitation of the epithelial to mesenchymal transition (EMT) [12]. Platelets, long recognized to have a role in facilitating metastasis, remain an intriguing target for intervention.

In Chap. 4, Joanna Roopkumar and Alok A. Khorana present the understanding of the risk of thrombosis in cancer. They present the clinical factors that are associated with increased risk of development of venous thrombosis. A number of clinical parameters are variably associated with increased risk, including advanced stage [13], cisplatin [14, 15], and central lines. However, the five key parameters

that have been incorporated into the widely validated "Khorana Score" for thrombosis risk in cancer, include (1) site of cancer, (2) prechemotherapy platelet count $\geq$ 350,000/mcL, (3) hemoglobin level < 10 g/dL or use of red cell growth factors, (4) prechemotherapy leukocyte count > 11,000/mcL, and (5) body mass index $\geq$ 35 kg/m^2 [16].

The rationale for the score is to achieve an optimal balance of benefit of anticoagulation thromboprophylaxis in risk reduction, with the burden of possible bleeding risk, cost, and inconvenience of anticoagulation. As Roopkumar and Khorana note, several trials studied a low-molecular-weight heparin (LMWH) with placebo control and demonstrated reduced risk of thrombosis, with non-significant increase in risk of bleeding [17, 18]. However, even though the studies were statistically significant, the baseline rate of thrombosis was low in both studies (3.4 and 3.9%), and therefore, the number needed to treat to achieve a clinically meaningful reduction in thrombosis was too high to justify introduction into practice. LMWH is expensive, and very uncomfortable to the patient, further discouraging use for a prophylactic setting.

The introduction of direct oral anticoagulants (DOAC), in conjunction with the Khorana Score, created a new opportunity to explore primary thromboprophylaxis. Two recent studies have now been completed and published, or presented, comparing apixaban or rivaroxaban to placebo in cancer patients with Khorana Scores of 2 or greater in ambulatory cancer patients [19, 20]. In the AVERT trial, apixaban decreased the rate of symptomatic venous thromboembolic events (VTE) from 10.2% in placebo to 4.2% ($p < 0.001$). There was a small, but significant increase in rate of major bleeding with apixaban (3.5% vs. 1.8%, $p = 0.046$) [19]. The CASSINI study of rivaroxaban versus placebo in cancer patients was presented at the American Society of Hematology convention in December 2018. The CASSINI study prescreened patients for pre-existing DVTs, and 4.53% had a DVT on baseline screening, explaining the lower event rate in the placebo arm. In CASSINI, while on drug, the rate of all VTE was reduced by rivaroxaban from 6.41 to 2.62% ($p = 0.007$). There was a small and non-significant increase in major bleeding with rivaroxaban (1.98% vs. 0.99%). These two studies suggest that with appropriate patient selection for Khorana Score of 2 or higher, primary thrombosis prophylaxis with a DOAC may be justified. We await guidance from the Food and Drug Administration, the National Comprehensive Cancer Network, and other regulatory bodies. In addition, the CASSINI study suggests that the baseline rate of DVT of approximately 4.5% in patients with Khorana Score of 2 or higher justifies screening ultrasound evaluation.

Chapter 5, Biomarkers of Cancer Associated Thromboembolism, by Anjlee Mahajan and Ten Wun, follows logically on the development and utilization of clinical parameters of the Khorana Score with the earlier discussion of the pathophysiology of cancer-associated thrombosis. The authors address the studies of biomarkers, which both reflect the mechanisms of enhanced thrombosis in cancer patients and possible use of these parameters to further improve the risk assessment.

There are a number of readily measurable coagulation and inflammation markers, associated with thrombosis in general, as well as in cancer patients in particular. These include C-reactive protein (CRP), tissue factor-expressing microparticles (TF-MP), D-dimer, soluble P-selectin (sP-selectin), plasminogen activator inhibitor 1 (PAI-1), Factor VIII, platelet count, and leukocyte counts.

The authors discuss the status of incorporating biomarkers into existing thrombosis risk scores, specifically sP-selectin and D-dimer by the Vienna CATS consortium [21]. They note, "identifying new easily measurable and analytically robust biomarkers remains an important goal to enhance risk assessment tools, and guide clinical decision-making." Thrombosis risk prediction, by clinical parameters as well as biomarkers, remains an important topic.

Beyond the thrombotic risk associated with cancer itself, cytotoxic chemotherapy and other cancer-directed treatments may in of themselves contribute to the thrombotic risk in patients with cancer. This is well addressed in Chap. 6, "Thrombotic Risk from Chemotherapy and Other Cancer Therapies," by Debbie Jiang and Alfred I. Lee. Systemic cancer therapy is estimated to increase thromboembolic risk by six- to sevenfold [22–24]. Tamoxifen, widely used in women with breast cancer, increases the risk of venous thrombosis, and possibly arterial thrombosis as well. Immunomodulatory imide drugs (IMiDs), such as thalidomide and lenalidomide, also significantly increase the risk of thrombosis in patients with myeloma. This effect has been recognized as sufficiently strong that this represents one of the first cancer situations where prophylactic anticoagulation has been routinely used, with aspirin, low-molecular-weight heparin, or warfarin [25, 26]. The monoclonal antibody to vascular endothelial growth factors (VEGF), bevacizumab, increases arterial and possibly venous thrombotic risk [27].

Cytotoxic chemotherapy may increase the risk of venous and/or arterial thrombosis. The chemotherapy drugs with the clearest association include cisplatin, fluorouracil, and L-asparaginase. The mechanisms of the increased thrombotic risk from chemotherapy are not clearly established; however, the authors discuss the current knowledge and limitations. They also address the recommendations for management.

The state of the art for treatment of VTE in cancer patients is discussed in Chap. 7, "Treatment of venous thromboembolism in cancer. Historical perspective and evolving role of the direct oral anticoagulants," by Marc Carrier, Gerald A. Soff, and Grégoire Le Gal. The authors provide historical context for treatment, first clarifying that use of vitamin K antagonists (VKA) has been shown particularly challenging in cancer patients. [28]. The CLOT study, published by Lee and colleagues in 2003, showed that LMWH was more effective than VKA for treatment of cancer-associated thrombosis [29]. This led to a major change in the standard of care for anticoagulation treatment of cancer-associated thrombosis, where LMWH has been widely accepted as the appropriate first-line therapy [30].

However, while LMWH has been the mainstay of treatment of CAT since 2003, recurrent thrombosis and major bleeding remain a significant risk (Table 1 of Chap. 7). Further, the discomfort of LMWH injections and the burden of high cost have been associated with poor compliance [31]. Two randomized clinical trials,

comparing a DOAC with LMWH, and several large case series evaluating DOACs for treatment of CAT have now been reported [32–38]. These reports support the use of a DOAC to treat CAT, with no reduction in efficacy, compared with LMWH. One important observation, derived from these studies, is that DOACs show a trend toward increased gastrointestinal and genitourinary tract bleeding in the presence of luminal pathology [32, 33].

Central venous access devices (CVADs) remain a widely used access device, throughout cancer management. In Chap. 8, "Etiology and Management of Upper Extremity Catheter Related Thrombosis in Cancer Patients," Anita Rajasekhar and Michael B. Streiff discuss thromboses associated with central venous access devices in oncology patients. As they note, thromboses may form on the different parts of the catheters, associated with different impacts on function and patient symptoms. The authors further discuss the factors associated with increased risk of catheter-related thrombosis (CRT) and the current understanding of the management of CRT.

While CRT is known to be common complications of central venous catheters and may lead to catheter failure or symptomatic upper extremity DVT, after reviewing the literature, they conclude that "*current evidence-based guidelines do not recommend routine thromboprophylaxis for cancer or non-cancer patients with CVADs*."

Thrombocytopenia is commonly observed in cancer patients, due to chemotherapy, marrow infiltration, radiation therapy, underlying hematopoietic stem cell disorders, infection, and other causes [39]. Thrombocytopenia in cancer, discussed in Chap. 9 "Management of Thrombocytopenia in Cancer Patients" by Jodi V. Mones and Gerald A. Soff, presents two particular challenges. The first is related to the consequence of chemotherapy-induced thrombocytopenia on delivery of full-dose chemotherapy. Chemotherapy-induced thrombocytopenia leads to delays and dose reduction of planned chemotherapy. Yet there remains no established, approved treatment. Mones and Soff review the current understanding of the problem and ongoing research to treat chemotherapy-induced thrombocytopenia.

A second topic discussed in Chap. 9 is management of anticoagulation in cancer patients with thrombocytopenia. This challenging situation arises when a cancer patient has both thrombocytopenia and is on anticoagulation for a thrombosis. The authors review the guidelines and recent validation of the guidelines.

The pathophysiologic syndrome thrombotic microangiopathy (TMA) may be observed in cancer patients, due to the underlying malignancy, cancer-related treatments, or an incidental diagnosis. Cancer-associated TMA is discussed in Chap. 10, "Microangiopathy in Cancer. Causes, Consequences, and Management," by Marie R. Thomas and Marie Scully. The authors discuss the important task of differential diagnosis and pathophysiology of the various TMA syndromes observed in the cancer population. The authors address early evidence of the possible role of eculizumab and other investigational agents for treatment of stem-cell-transplant-related TMA, although there is no established guidelines for if and when to use these agents.

In Chap. 11, Kamya Sankar, Brady L Stein, and Raajit K. Rampal address the pathophysiology of "Thrombosis in the Philadelphia Chromosome-Negative

Myeloproliferative Neoplasms." As the authors note, the myeloproliferative neoplasms (MPNs) are clonal stem-cell-derived diseases which "are associated with both microvascular and macrovascular thrombosis, which may occur in the venous and arterial circulation." The MPNs are typically due to driver mutations which activate the JAK-STAT pathway (most commonly JAK2V617F, followed by CALR and MPL mutations) and are some of the most prothrombotic neoplastic disorders [40]. Beyond the classic deep vein thrombosis and pulmonary embolism, MPNs are associated with thromboses of hepatic vein, portal vein, splenic vein, or mesenteric veins as well as microvascular thrombosis resulting in livedo reticularis, erythromelalgia, and other characteristic complications. The authors address the role of the underlying driver mutation, as well as other clinical parameters, influencing the risk of thrombosis.

Management of thrombosis risk in MPN is based on risk assessment, risk reduction by cytoreduction, and prophylactic anticoagulation in selected patients. The authors note, "Anticoagulation therapy is indicated for those patients who develop venous thrombosis. The choice of anticoagulant and appropriate duration of therapy, however, is unclear." The existing data on potential role for the direct oral anticoagulants is also discussed, but this body of data also remains insufficient to provide definitive guidance.

Use of anticoagulants in patients with primary or metastatic cancer in the brain is always a situation resulting in great anxiety on the part of the patient and treating physician. This is addressed in Chap. 12, "Anticoagulation in the setting of primary and metastatic brain tumors," by authors Charlene Mantia and Jeffrey I. Zwicker. As the authors note, patients with gliomas and metastatic cancer to the brain are at very high risk of thrombosis, and yet also have a high baseline risk of intracranial hemorrhage. There are few clinical scenarios where balancing the risk and benefit of anticoagulation is as great.

The authors review the existing literature on the scope of the problem and current understanding of when and in which situations to use anticoagulation. They note that although the baseline risk of intracranial hemorrhage from metastatic cancer is high, "*In patients with brain metastases, low molecular heparin does not increase the rates of intracranial hemorrhage*." This provides some reassurance in managing these complex patients, in challenging situations.

In contrast, they note that anticoagulation does appear to increase the risk of intracranial hemorrhage in patients with glioma. Their explicit words of caution are, "*In light of the current evidence suggesting an increased rate of intracranial hemorrhage in patients with glioma, judicial use of therapeutic anticoagulation is warranted. We advise a careful consideration of risk factors for hemorrhage in glioma. Until more data becomes available, it is reasonable to consider full dose anticoagulation with careful monitoring or alternative strategies that may include dose-modification of anticoagulants and/or placement of IVC filters in those patients at greatest risk for hemorrhage*."

In the last chapter of this book, Chap. 13, "Bleeding Disorders Associated with Cancer," Simon Mantha, MD discusses several hemorrhagic syndromes associated

with cancer. While none of these syndromes are common, prompt recognition and appropriate intervention may have a great impact on patient survival.

The primary hyperfibrinolytic syndrome associated with acute promyelocytic leukemia has been well recognized and is one of the most severe bleeding disorders. Prompt recognition of this life-threatening hemorrhagic disorder is critical, as delay in diagnosis and appropriate intervention may be associated with critical bleeding and death in a patient population with an otherwise good prognosis. Acquired hemophilia, while rare, may be precipitated by cancer. Acquired hemophilia also requires prompt recognition, as effective therapy is now available. Other topics discussed include the various malignancies that are associated with acquired von Willebrand disease, the role of leukostasis, paraproteins and hyperviscosity, amyloidosis, and drug effects. While none of these syndromes are common, familiarity with the presentations, diagnostic criteria, and appropriate management is a critical body of knowledge for any provider involved in care for patients with cancer.

This is indeed a very exciting time to be involved in the field of "Thrombosis and Hemostasis in Cancer." In some ways, this is a very old area of study, representing the first paraneoplastic syndrome, eloquently described by Armond Trousseau over 150 years ago. In other ways, it is a new and rapidly evolving field, incorporating new understandings of pathophysiology, diagnostic tools, and most importantly, improving treatment. This is best illustrated in a true, "stop the presses" moment, when Chap. 4, on "Risk of Thrombosis in Cancer: Clinical Factors and Role of Primary Prophylaxis," was revised on the eve of going to press, to allow for incorporation of exciting new results in the role of primary thrombosis prophylaxis.

The ongoing progress in understanding of the pathophysiology, clinical manifestations, and appropriate treatment of disorders of thrombosis and hemostasis in cancer is leading to improved care and outcomes. On behalf of all the authors who have contributed to this book, we hope that our work will serve as a helpful contribution.

References

1. Samuels MA, King ME, Balis U (2002) Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 31-2002. A 61-year-old man with headache and multiple infarcts. N Engl J Med 347(15):1187–1194
2. De Bouillaud S (1823) lÕObliteration des veines et de son influence sur la formation des hydropisies partielles: consideration sur la hydropisies passive et general. Arch Gen Med 1:188–204
3. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH (2007) Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost 5(3):632–634
4. Falanga A, Marchetti M (2009) Venous thromboembolism in the hematologic malignancies. J Clin Oncol 27(29):4848–4857
5. Piccioli A, Falanga A, Baccaglini U, Marchetti M, Prandoni P (2006) Cancer and venous thromboembolism. Semin Thromb Hemost 32(7):694–699
6. Gasic GJ, Gasic TB, Murphy S (1972) Anti-metastatic effect of aspirin. Lancet 2(7783): 7932–7933

7. Gasic GJ, Gasic TB, Stewart CC (1968) Antimetastatic effects associated with platelet reduction. Proc Natl Acad Sci USA 61:46–52
8. Leader A, Zelikson-Saporta R, Pereg D, Spectre G, Rozovski U, Raanani P et al (2017) The effect of combined aspirin and clopidogrel treatment on cancer incidence. Am J Med 130 (7):826–832
9. Liang HW, Yan X, Pan Y, Wang YS, Wang N, Li LM, et al (2015) MicroRNA-223 delivered by platelet-derived microvesicles promotes lung cancer cell invasion via targeting tumor suppressor EPB41L3. Mol Cancer 14
10. Donatelli SS, Zhou JM, Gilvary DL, Eksioglu EA, Chen XH, Cress WD et al (2014) TGF-beta-inducible microRNA-183 silences tumor-associated natural killer cells. Proc Natl Acad Sci USA 111(11):4203–4208
11. Laffont B, Corduan A, Rousseau M, Duchez AC, Lee CHC, Boilard E et al (2016) Platelet microparticles reprogram macrophage gene expression and function. Thromb Haemost 115 (2):311–323
12. Tang ML, Jiang L, Lin YY, Wu XL, Wang K, He QZ et al (2017) Platelet microparticle-mediated transfer of miR-939 to epithelial ovarian cancer cells promotes epithelial to mesenchymal transition. Oncotarget 8(57):97464–97475
13. Agnelli G, Bolis G, Capussotti L, Scarpa RM, Tonelli F, Bonizzoni E et al (2006) A clinical outcome-based prospective study on venous thromboembolism after cancer surgery: the @RISTOS project. Ann Surg 243(1):89–95
14. Moore RA, Adel N, Riedel E, Bhutani M, Feldman DR, Tabbara NE et al (2011) High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: a large retrospective analysis. J Clin Oncol 29(25):3466–3473
15. Starling N, Rao S, Cunningham D, Iveson T, Nicolson M, Coxon F et al (2009) Thromboembolism in patients with advanced gastroesophageal cancer treated with anthracycline, platinum, and fluoropyrimidine combination chemotherapy: a report from the UK National Cancer Research Institute Upper Gastrointestinal Clinical Studies Group. J Clin Oncol 27(23):3786–3793
16. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW (2008) Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 111 (10):4902–4907
17. Agnelli G, George DJ, Kakkar AK, Fisher W, Lassen MR, Mismetti P et al (2012) Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. N Engl J Med 366(7):601–609
18. Agnelli G, Gussoni G, Bianchini C, Verso M, Mandala M, Cavanna L et al (2009) Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. Lancet Oncol 10(10):943–949
19. Carrier M, Abou-Nassar K, Mallick R, Tagalakis V, Shivakumar S, Schattner A, et al (2018) Apixaban to prevent venous thromboembolism in patients with cancer. N Engl J Med
20. Khorana AA, Soff GA, Kakkar AK, Vadhan-Raj S, Riess H, Wun T, et al (2018) Rivaroxaban thromboprophylaxis in high-risk ambulatory cancer patients receiving systemic therapy: results of a randomized clinical trial (CASSINI) (Abstract). Blood
21. Ay C, Dunkler D, Marosi C, Chiriac AL, Vormittag R, Simanek R, et al (2010) Prediction of venous thromboembolism in cancer patients. Blood
22. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd (2000) Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med 160(6):809–815
23. Khorana AA, Dalal M, Lin J, Connolly GC (2013) Incidence and predictors of venous thromboembolism (VTE) among ambulatory high-risk cancer patients undergoing chemotherapy in the United States. Cancer 119(3):648–655
24. Lyman GH, Khorana AA, Falanga A, Clarke-Pearson D, Flowers C, Jahanzeb M et al (2007) American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. J Clin Oncol 25(34):5490–5505

25. Knight R, DeLap RJ, Zeldis JB (2006) Lenalidomide and venous thrombosis in multiple myeloma. N Engl J Med 354(19):2079–2080
26. Larocca A, Cavallo F, Bringhen S, Di Raimondo F, Falanga A, Evangelista A, et al (2012) Aspirin or enoxaparin thromboprophylaxis for patients with newly diagnosed multiple myeloma treated with lenalidomide. Blood 119(4):933–939; quiz 1093
27. Zangari M, Fink LM, Elice F, Zhan F, Adcock DM, Tricot GJ (2009) Thrombotic events in patients with cancer receiving antiangiogenesis agents. J Clin Oncol 27(29):4865–4873
28. Prandoni P, Lensing AW, Piccioli A, Bernardi E, Simioni P, Girolami B et al (2002) Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 100(10):3484–3488
29. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M et al (2003) Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 349(2):146–153
30. Streiff MB, Holmstrom B, Ashrani A, Bockenstedt PL, Chesney C, Eby C, et al (2015) Cancer-associated venous thromboembolic disease, version 1.2015. J Natl Compr Canc Netw 13(9):1079–1095
31. Khorana AA, Yannicelli D, McCrae KR, Milentijevic D, Crivera C, Nelson WW et al (2016) Evaluation of US prescription patterns: Are treatment guidelines for cancer-associated venous thromboembolism being followed? Thromb Res 145:51–53
32. Mantha S, Laube E, Miao Y, Sarasohn DM, Parameswaran R, Stefanik S et al (2017) Safe and effective use of rivaroxaban for treatment of cancer-associated venous thromboembolic disease: a prospective cohort study. J Thromb Thrombolysis 43(2):166–171
33. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D et al (2018) Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 378(7): 615–624
34. Young A, Marshall A, Thirlwall J, Hill C, Hale D, Dunn J, et al (2017) Anticoagulation therapy in selected cancer patients at risk of recurrence of venous thromboembolism: results of the select-D pilot trial. In: ASH 59th annual meeting & exposition. Blood, Atlanta, GA, p. 625
35. Ross JA, Miller MM, Rojas Hernandez CM (2017) Comparative effectiveness and safety of direct oral anticoagulants (DOACs) versus conventional anticoagulation for the treatment of cancer-related venous thromboembolism: a retrospective analysis. Thromb Res 150:86–89
36. Seo SR, M-H, Kang Y-K, Kim K-P, Chang H-M, Ryoo B-Y, Kim SB, Lee J-L, Park SR (2016) Oral rivaroxaban versus subcutaneous low molecular weight heparin treatment for venous thromboembolism in patients with upper gastrointestinal, hepatobiliary and pancreatic cancer. Ann Oncol 27(Suppl 6):695
37. Streiff MB, Milentijevic D, McCrae K, Yannicelli D, Fortier J, Nelson WW et al (2018) Effectiveness and safety of anticoagulants for the treatment of venous thromboembolism in patients with cancer. Am J Hematol 93(5):664–671
38. Theberge I, Bowdridge J, Forgie MA, Carrier M, Louzada M, Siquiera L et al (2017) Rivaroxaban shows promise as effective therapy for cancer patients with venous thromboembolic disease. Thromb Res 152:4–6
39. Mantha S, Miao Y, Wills J, Parameswaran R, Soff GA (2017) Enoxaparin dose reduction for thrombocytopenia in patients with cancer: a quality assessment study. J Thromb Thrombolysis 43(4):514–518
40. Tefferi A, Vainchenker W (2011) Myeloproliferative neoplasms: molecular pathophysiology, essential clinical understanding, and treatment strategies. J Clin Oncol 29(5):573–582

Pathophysiology 1. Mechanisms of Thrombosis in Cancer Patients

2

Anna Falanga, Francesca Schieppati and Laura Russo

Contents

A. Falanga (✉) · F. Schieppati · L. Russo
Department of Transfusion Medicine and Hematology, Hospital Papa Giovanni XXIII, Bergamo, Italy
e-mail: annafalanga@yahoo.com; afalanga@asst-pg23.it

A. Falanga
University of Milan Bicocca, School of Medicine and Surgery, Monza, Italy

G. Soff (ed.), *Thrombosis and Hemostasis in Cancer*, Cancer Treatment and Research 179, https://doi.org/10.1007/978-3-030-20315-3_2

2.1 Introduction

The close relationship between cancer and thrombosis has been known for more than a century. Cancer patients present with many types of hemostatic abnormalities and have an increased risk of both thrombotic and hemorrhagic complications. A very intimate and reciprocal relation exists between malignant disease, the occurrence of clotting alterations and thrombosis. Indeed, malignancy most commonly induces a procoagulant shift in the host hemostatic balance [1], thus establishing a condition favorable to the development of thrombosis. Vice versa, the activation of blood coagulation favors the tumor growth and dissemination.

Cancer is associated with a four- to sevenfold increase in the risk of venous thromboembolism (VTE) [2, 3], peaking in the first 3 months following cancer diagnosis [4, 5]. The risk of thrombosis is also increased in metastatic compared with non-metastatic cancer disease. However, even without thrombosis, the majority of cancer patients present with clotting alterations detectable by laboratory tests, which reveal different degrees of coagulation activation and characterize the hypercoagulable state of these subjects [6]. Currently, it is fully recognized that cancer patients are at significant risk of developing all types of thrombotic events, spanning from venous or arterial thrombosis to systemic syndromes, such as disseminated intravascular coagulation (DIC) with severe bleeding. Preventing these complications is clinically relevant because they considerably contribute to the morbidity and mortality of these patients [7].

The pathogenesis of the cancer-associated thrombosis (CAT) is complex and multifactorial. Many clinical factors influence the thrombotic risk of these patients. Clinical factors include general risk factors (i.e., older age, cardiovascular diseases, prior VTE, infections, prolonged immobilization), as well as disease-specific factors, as the cancer site and stage and anticancer therapies. Further, biological mechanisms are involved in the pathogenesis of CAT. Indeed, tumor cells gain the capacity to activate the host hemostatic system in several ways, and this phenomenon is often driven by the same oncogenes responsible for the cellular neoplastic transformation [8]. By this process, cancer tissues become able to express different procoagulant proteins (i.e., tissue factor [TF], cancer procoagulant [CP], factor VII) and to shed procoagulant microparticles. Furthermore, they activate platelets, leukocytes, and endothelial cells, by direct cell–cell adhesion mechanisms, or through the liberation of inflammatory cytokines or proangiogenic factors. All these phenomena contribute to the pathogenesis of CAT.

In this chapter, we wish to review the most recent advances in our knowledge on the pathogenic factors underlying the development of thrombosis in patients with malignant diseases, with a particular focus on the cancer tissue-specific biological properties, by which malignant cells are capable to activate the hemostatic system.

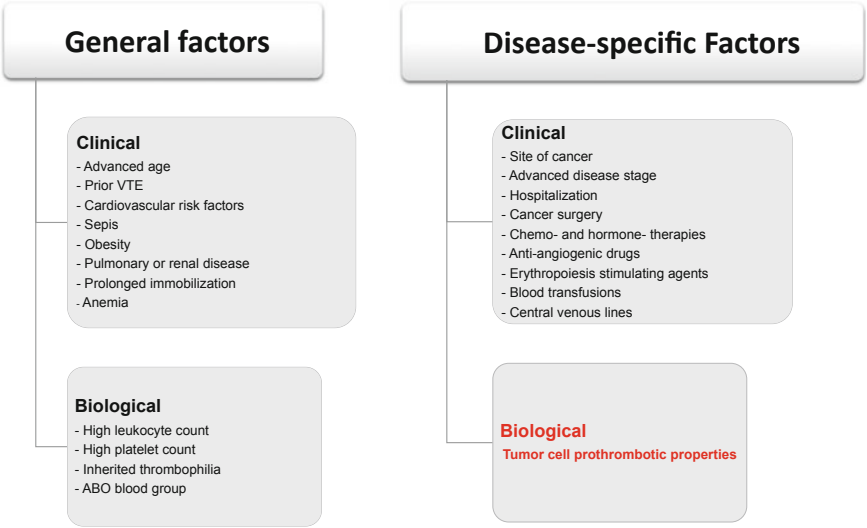

Fig. 2.1 Pathogenesis of thrombophilic state in cancer patients is multifactorial. Clinical risk factors include general and biological factors, which are common to cancer and non-cancer patients, whereas in patients with malignancy there are also a number of disease-specific clinical as well biological factors. Particularly, a unique role is played by the capacity of tumor cells to interact and activate blood coagulation

2.2 Pathogenic Factors of Cancer-Associated Thrombosis

Multiple clinical factors together with biological procoagulant mechanisms expressed by cancer tissues concur to the activation of blood coagulation and importantly contribute to the overall thrombotic risk of these patients [9, 10] (Fig. 2.1). Clinical risk factors include general and biological factors, which are common to cancer and non-cancer patients, whereas in patients with malignancy there are also a number of disease-specific clinical as well biological factors, which render the pathogenesis of cancer-associated thrombosis unique.

Altogether, these factors favor the shift of the hemostatic balance toward a prothrombotic condition, as shown by the appearance of subclinical coagulation changes in almost all of cancer patients, who constantly present with high levels of circulating biomarkers of hypercoagulability.

2.2.1 General Factors

General factors include both clinical and biological risk factors, which are common to all patients, with and without cancer.

As listed in Fig. 2.1, general clinical factors include older age, prior history of VTE, prolonged immobilization, obesity, infections, cardiovascular risk factors, renal and respiratory diseases, and anemia.

On the other hand, biological factors carrying a thrombotic risk in the general population comprise high leukocyte and platelet counts, the inherited thrombophilia, and the ABO blood group.

In particular, elevated numbers of platelets and neutrophils are often observed in patients with cancer, and several studies have demonstrated their association with an increased risk of thrombosis [11, 12], and with a poor cancer prognosis [13]. It is possible that granulocyte colony-stimulating growth factor (G-CSF), produced by many tumors and present in the circulation of many cancer patients, contributes to increase the number of neutrophils and induce their activation [13]. The "Khorana risk model," an important tool that predicts the risk of cancer-associated thrombosis, includes pretreatment thrombocytosis (platelet count $\geq 350 \times 10^9$/L) and leukocytosis (leukocytes $\geq 11 \times 10^9$/L) among the five clinical risk factors associated with an increased risk of VTE, together with the site of cancer, hemoglobin < 10 g/dl, and a body mass index ≥ 35 kg/m^2 [14]. These findings have now been validated by many other large studies [15–17].

The role of prothrombotic genotypes has been considered in cancer patients [18]. The influence of inherited thrombophilia in patients with cancer may be more difficult to demonstrate than in the general population, the risk of thrombosis due to cancer per se possibly outweighing the contribution of thrombophilia factors. However, in the presence of cancer, prothrombotic genotypes may further increase the thrombotic risk [19]. Several studies evaluating the role of factor V Leiden or G202110A prothrombin gene mutation on the risk of CAT have been published [20]. Overall, although conflicting results were obtained, it appears that patients with cancer and either of these mutations tend to exhibit a higher risk of thrombosis than patients with cancer without these mutations. Indeed, in recent large studies the risk of VTE of patients with both cancer and **factor V Leiden** mutation was increased from 2 to 12-fold, compared to patients without factor V Leiden [5, 21, 22]. Studies investigating on the impact of **prothrombin 20210A** mutation on the risk of cancer-related VTE have shown conflicting results, possibly due to the rarity of this mutation. However, a large study found that patients with cancer and prothrombin 20210A mutation had a fourfold increased risk of VTE compared to the non-carriers with cancer and an 18-fold increase compared to cancer-free non-carriers [5]. Similar results were reported for central venous catheter-related VTE [23].

Finally, an association between **ABO blood groups** and the risk of VTE has also been described since 1969, being non-O blood groups associated to an increased risk of VTE [24], particularly type A1 and B groups [25]. The single-nucleotide polymorphism (SNP) rs8176719 represents a site in the ABO gene essential to determine the O group and has been used to evaluate the risk of cancer-related VTE in a case–control study [22]. In cancer patients, a non-O blood type was associated with a 30% increased risk of VTE, and even higher risk (12-fold increased) if compared to cancer-free subjects with an O blood type [22].

2.2.2 Disease-Specific Factors

In this category are clinical and biological pathogenic factors that are exclusive to the malignant disease (Fig. 2.1).

Clinical factors undoubtedly include the site of cancer. Indeed, large epidemiological studies have recognized brain tumors, hematological malignancies, and pancreatic, gastric, ovarian, uterus, pulmonary and renal adenocarcinomas as having the highest risk of VTE [26]. Among hematological malignancies, multiple myeloma, Hodgkin's disease, and non-Hodgkin lymphoma have shown the highest incidence of VTE [27].

The stage of cancer is also an important risk factor for VTE; advanced, metastatic disease is linked to a higher risk of VTE compared to localized tumors [26]. The initial period after diagnosis of cancer is at high risk of VTE as well [5].

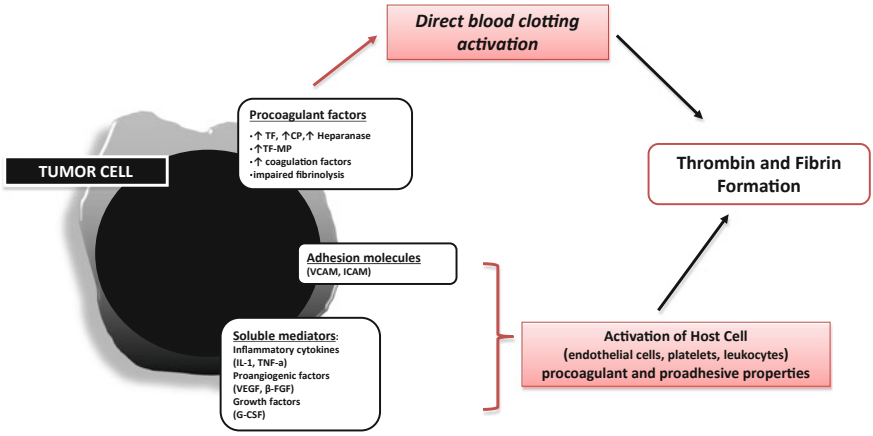

Fig. 2.2 Principal mechanisms of hypercoagulability in cancer. Direct blood clotting activation by the expression of hemostatic proteins with procoagulant activity by cancer cells; host cell-cancer cell interaction, through the expression of surface adhesion molecules and through the release of soluble mediators, including inflammatory cytokines and proangiogenic and growth-stimulating factors

Finally, active anticancer treatments, such as chemo-, radio-, and hormone therapies, antiangiogenetic agents, combination regimens, cancer surgery, the use of erythropoiesis-stimulating agents and blood transfusions exert a prothrombotic effect [28]. Chemotherapeutic agents and tumor-derived products can directly damage the vascular endothelium, leading to a loss of endothelial antithrombotic properties [28]. Moreover, chemotherapy can induce an overexpression of tissue factor, an increased exposure of cell membrane phosphatidylserine, and the release of procoagulant microparticles [29]. All these mechanisms, as well as the presence of central venous lines to deliver drugs and nutrients, can play a role in the pathogenesis of CAT.

2.3 Cancer Cell Prothrombotic Mechanisms

The principal procoagulant mechanisms expressed by cancer cells are schematically depicted in Fig. 2.2 and include:

1. The activation by cancer cells of the clotting system through the expression of procoagulant properties (such as tissue factor [TF], cancer procoagulant [CP], and heparanase), TF-bearing procoagulant microparticles (TF-MP), coagulation factors, and fibrinolysis proteins;
2. The activation by cancer cells of the procoagulant potential of host blood vascular cells, i.e., platelets, leukocytes, and endothelial cells. The latter mechanism can occur either by cell–cell direct contact mediated by specific surface adhesion receptors, and/or by the release of inflammatory cytokines, and proangiogenic and growth-stimulating factors (i.e., vascular endothelial growth factor [VEGF], basic fibroblast growth factor [bFGF], and G-CSF) by both cancer and host blood cells. The activation of platelets, endothelial cells, and leukocytes produces, among other procoagulant features, the release of blood cell-specific procoagulant microparticles (MP) and neutrophil extracellular traps (NETs).

2.3.1 Cancer Cell Procoagulant Properties

The procoagulant properties expressed by cancer cells include:

- procoagulant proteins,
- microparticles (MPs),
- coagulation factors,
- fibrinolysis proteins.

2.3.1.1 Cancer Cell Procoagulant Proteins

Among procoagulant proteins, **tissue factor (TF)** is the best characterized. TF is the primary initiator of blood coagulation in normal and pathological conditions. It forms a complex with activated factor VII to trigger blood coagulation by proteolytic activation of factors IX and X (clotting extrinsic pathway). Many solid tumors and hematologic malignancies constitutively express TF, and the levels of TF expression tend to be associated with an aggressive pattern of the tumor. Indeed, studies performed in malignant gliomas and pancreatic tumors demonstrated that the levels of TF expression correlate with the histological grade of malignancy and vascularity [30–34]. Moreover, TF activity can be potentiated by the expression of anionic phospholipids on the outer leaflet of glioma cells, leading to coagulation reactions through the intrinsic pathway and to explosive generation of thrombin [35]. Other studies conducted in colorectal and pancreatic cancers show that plasma levels of TF antigen correlate with the tumor size [36, 37]. TF expression by tumor cells is a consequence of cancer-causing mutations, like oncogenes activation (i.e., *KRAS* and *MET*) or tumor suppressor genes inactivation (i.e., *p53*, *PTEN*) [38]. The elevated inflammatory status of cancer patients also enhances TF production. Indeed, endothelial cells and monocyte/macrophages that do not express TF under normal conditions can be induced to express TF by proinflammatory stimuli (i.e., IL-1β, TNF-α, and bacterial lipopolysaccharides [LPS]) [39].

Tumor-cell-derived TF plays a central role in the generation of thrombin in cancer, but also contributes to tumor progression by directly influencing the expression of VEGF by both malignant cells and host vascular cells. This property regulates tumor neovascularization and provides an important link between activation of coagulation, inflammation, thrombosis, and tumor growth and metastasis [1].

Another tumor cell procoagulant is **cancer procoagulant** (**CP**) that, unlike TF, directly activates factor X independently of coagulation factor VII. CP has been detected in different malignant cells [40], from both solid and hematologic tumors, but not in normal tissues. Of interest, in patients with acute promyelocytic leukemia (APL), CP is expressed by bone marrow blast cells at the onset of disease, but disappears at remission [41]. In addition, in APL patient blasts, CP expression paralleled the degree of malignant transformation and disappeared upon cellular differentiation by therapy with all-trans-retinoic-acid (ATRA). In contrast, cells resistant to ATRA maintained their malignant phenotype and continue to express CP. Similar observations have been reported for breast cancer [42]. The relative contribution of this factor to the overall cellular procoagulant activity and/or possible interactions with TF are unknown at this time.

Among other tumor cell procoagulant activities, the role of the enzyme **heparanase** is gaining much relevance. Heparanase is a protease that cleaves heparan sulfate (HS) of the extracellular matrix (ECM). Its expression is restricted to platelets, activated white blood cells, and placenta. Many studies demonstrated an overexpression of this enzyme in essentially all human tumors, both solid and hematological [43], which promotes tumor dissemination and metastasis, by remodeling ECM barrier [44, 45], releasing VEGF-A and bFGF bound to HS [46,

47], and by facilitating endothelial cells migration and proliferation [48, 49]. Additionally, it upregulates the expression of the blood coagulation initiator TF and interacts with the tissue factor pathway inhibitor (TFPI) on the cell surface of endothelial and tumor cells, leading to dissociation of TFPI with resulting increased cell surface TF activity [50]. Finally, heparanase directly activates the extrinsic coagulation pathway, increasing the level of factor Xa in the presence of TF/VIIa, acting as a cofactor of TF [50].

2.3.1.2 Tumor Microparticles

Tumor-cell-shed **microparticles (MP)** represent an emerging mechanism of tumor-promoted clotting activation. MP are plasma membrane vesicles of 0.1–1 μm in diameter, composed of lipids, proteins, and nucleic acids, released from virtually all types of blood cells upon activation, apoptosis, malignant transformation, and stress [51]. MP display typical surface cell proteins derived from the cell of origin, but they can also carry proteins acquired from other cell types by a fusion process. Platelet-derived MP (PMP) constitute the majority (>80%) of circulating MP, whereas less than 10% originate from granulocytes and less than 5% from endothelial cells, red blood cells, and monocytes. However, in pathological conditions, an overall increment of MP occurs also from other sources, including tumor cells. Under normal conditions, MP express anionic phosphatidylserine (PS) on their outer leaflet, though several reports show that a subset of circulating PMP may also express TF [52]. In healthy individuals, the majority (>95%) of circulating PMP express PS, whereas only a very low number express TF, and circulate at low levels. MP undergo phenotypic and quantitative changes in several clinical conditions, most of which associated with an increased risk of both arterial and venous thrombosis (i.e., diabetes, acute coronary syndrome, disseminated intravascular coagulation, antiphospholipid syndrome) [53–56]. The increased number and thrombogenic activity of MP in prothrombotic disorders indicate their important role in the pathogenesis of thrombosis. In the cancer setting, TF-bearing MP are of particular interest, since, due to the abundance of negatively charged phospholipids on their surface, they display TF in its "active" form. Elevated levels of circulating MP have been described in cancer patients, with both solid and hematologic malignancies [57, 58], and different reports suggest an additional role for these elements in the establishment of a thrombotic state in cancer [59–61]. Several studies demonstrated that TF-positive MP can be derived from tumor cells. The increased production of MP by cancer cells seems to be controlled by definite genetic events occurring in tumorigenesis, including activating and inactivating mutations in oncogenes and tumor repressor genes [62]. Studies in animal and human models showed that tumor-derived TF-positive MP contribute to cancer-associated thrombosis [63–66]. The intravenous injection into mice of MP derived from human tumor cells and expressing high levels of TF induced a TF-dependent activation of coagulation, which resulted in a DIC-like syndrome [37]. Elevated TF-positive MP have been reported in patients with solid tumors and VTE gastric and pancreatic cancers being the most studied [59, 61, 67]. Fewer reports have been published in the setting of hematological malignancies, where

high levels of blast cell-derived MP have been confirmed in acute promyelocytic leukemia [68] and acute myeloid leukemia [69]. In patients with multiple myeloma, TF-positive MP activity was higher in those developing VTE [70]. In one study of essential thrombocythemia (ET), MP numbers were significantly higher in ET patients than controls, and the thrombin generation potential of MP-rich plasma from these patients was significantly increased [71].

MP can also play a role in cancer progression, especially due to their capacity to influence angiogenesis [72]. In one study, it has been shown that PMP isolated from healthy donors can promote proliferation, survival, and capillary tube formation of human endothelial cells [73]. In addition, PMP can stimulate the expression of proangiogenic factors by tumor cells [74]. Finally, the expression of TF by circulating MP represents per se an important mechanism of MP-promoted tumor progression, by means of TF role in tumor growth, angiogenesis, and metastasis [75–77].

The clinical significance of MP as a predictive biomarker of VTE risk in cancer patients has not been fully elucidated. For this reason, some trials are evaluating the utility of measuring TF-MP to predict VTE in cancer [78]. Since MP are clearly involved in thrombosis and cancer, potential modulation of their release and activity may have important therapeutic implications.

2.3.1.3 Coagulation Factors

The plasma protein **factor VII (FVII)**, under normal conditions, is constitutively expressed in the liver, mainly by hepatocytes [79]. However, FVII can be expressed also by monocytes and macrophages in inflammatory conditions [80, 81], and in cancer, where the expression of ectopic FVII has been described in hepatocellular carcinoma cells [82], bladder cancer [83], ovarian cancer [84], and laryngeal carcinoma [85]. More recent studies on FVII mRNA expression in different cancer cell lines have demonstrated a frequent expression of endogenous FVII in various cancer cells [86], especially in colon cancer cell lines [87]. In these experiments, ectopic FVII was functionally active due to cancer cell expression of γ-glutamyl carboxylase, which facilitates the post-translational edits required for proper positioning of FVII on the cell membrane [86]. Coagulant-active ectopically expressed TF:FVIIa was also found on TF-positive ovarian cancer cells, making this complex a plausible trigger of VTE at distant sites, which is a frequent complication in patients with ovarian cancer [88].

Factor VIII (FVIII) plays a key role in the coagulation cascade. Several studies have shown that high factor VIII activity indicates an increased risk for primary and recurrent venous thromboembolism [89, 90]. High FVIII levels have been observed in patients with multiple myeloma, breast cancer, and colorectal cancer [91–93]. A small retrospective study reported higher FVIII levels in patients with various types of cancer and a history of thrombosis in comparison to a matched control group without thrombosis [94]. A subsequent prospective cohort study confirmed that high FVIII plasma level is a significant risk factor for symptomatic VTE in cancer patients [95]. In this study, the risk conferred by FVIII correlated with the FVIII levels. A significant difference in FVIII according to the tumor site was described, being FVIII levels highest in cancers of the stomach or pancreas, in

which an association with disease stage was also seen. Similar findings were reported in patients with multiple myeloma [91]. However, to what extent the malignant disease contributes to FVIII plasma levels needs to be further elucidated.

2.3.1.4 Fibrinolysis Proteins

In this context, it is important to consider that tumor cells also generate anticoagulant forces and interact with the **host fibrinolytic system**. Indeed, cancer cells can express fibrinolytic proteins such as the plasminogen activators [i.e., urokinase-type plasminogen activator (uPA) and tissue-type plasminogen activator (tPA)], their inhibitors [i.e., plasminogen activator inhibitor-1 (PAI-1) and plasminogen activator inhibitor-2 (PAI-2)], and receptors (i.e., urokinase-type plasminogen activator receptor, and annexin II, a co-receptor for plasminogen and tPA). Elevated levels of PAI-1 antigen and activity have been found in patients with pancreatic cancer and malignant glioma [96, 97], predisposing to VTE. In a mouse model xenografted with a human lung adenocarcinoma cell line, the anti-VEGF drug, bevacizumab, induced an increase in PAI-1 levels and enhanced thrombosis, which was reduced by a PAI-1 inhibitor [98]. In APL, the increased annexin II expression by leukemic cells favors the assembly of the fibrinolytic cascade proteins on the cell surface and has been linked to excessive activation of fibrinolysis and bleeding complications [99].

Likely, depending on which side, pro- or antifibrinolytic, prevails, the clinical manifestations may be quite different, from bleeding symptoms, as observed in leukemia, to VTE, as evidenced in solid tumors.

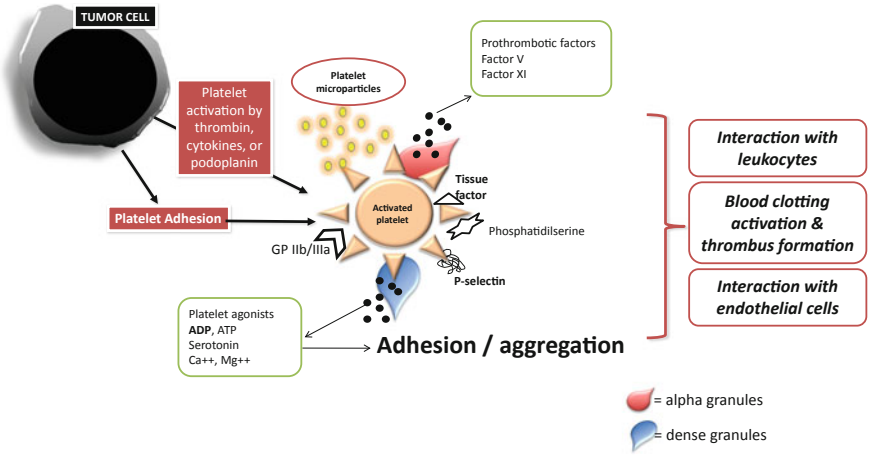

Fig. 2.3 Platelet activation by tumor cells. Tumor cells activate platelets through direct cancer cell–platelet adhesion, tumor secretion of platelet-activating molecules or by the expression of podoplanin on cancer cells' surface. Activated platelets can mediate the onset of hypercoagulability in cancer patients by direct clotting activation and thrombus formation or by interacting with other blood cells

2.3.2 Host Cell Procoagulant Properties Elicited by Cancer Cells

A strong interaction occurs between cancer cells and the host normal vascular cells, particularly **platelets**, **leukocytes**, and **endothelial cells**, which generally results in the expression of a procoagulant phenotype by normal cells. As schematically shown in Fig. 2.2, cancer cells activate the procoagulant potential of host normal vascular cells by two principal mechanisms, i.e., (1) the expression by cancer cells of surface adhesion molecules and counter-receptors by which they anchor other blood cells and attach to the vessel wall and (2) the release of soluble mediators, including inflammatory cytokines (i.e., TNF-α, IL-1β), proangiogenic and growth-stimulating factors (i.e., VEGF, bFGF, G-CSF), and platelet aggregation agonists.

2.3.2.1 Platelets' Activation by Tumor Cells

There is growing evidence that platelets are very important in promoting the hypercoagulable state of patients with cancer [100]. However, a fundamental step occurring in malignancy is platelet activation by direct cancer cell–platelet adhesion [17, 100, 101], and/or by tumor secretion of platelet-activating molecules (i.e., ADP, thrombin, matrix metalloproteinases, IL-6) [102], which lead to platelet adhesion/aggregation (Fig. 2.3). Among adhesion mechanisms, selectins expressed on platelets, leukocytes, and endothelium can bind tumor cells to form aggregates [103]. Specifically, P-selectin expressed on the surface of activated platelets binds to many types of human cancer cells [104], and this interaction can also promote tumor growth and metastasis [104]. In general, platelet activation, aggregation, coagulation, and thrombus formation are crucial events in limiting blood loss after tissue damage but are also major determinants of hematogenous tumor metastasis [105]. Increased platelet activation and aggregation correlate with the metastatic potential of cancer cells in both in vitro and in vivo models of experimental metastasis. Indeed, platelet aggregation protects the tumor cell surface from immunological recognition in the circulation. Tumor-cell-induced platelet aggregation can result in a "platelet coating" of cancer cells shielding them from natural killer (NK) cells [106]. Some tumor cells may use podoplanin, a transmembrane sialoglycoprotein, to activate platelets [107]. Podoplanin is a ligand of the platelet receptor C-type lectin receptor type-2 (CLEC-2) and induces platelet aggregation in normal conditions. Podoplanin is present on the surface of certain tumor cells, including melanoma, squamous cell carcinoma, seminoma, and brain tumor cells [107]. Increased levels of podoplanin are associated with tumor metastasis or malignant progression, however, recent data clearly show that podoplanin-positive MP from brain tumors activate circulating platelets, and are associated with platelet aggregation and increased thrombotic risk in these patients [108]. Strategies are now being developed to inhibit podoplanin–CLEC2 interactions in preclinical models of solid tumors [109].

Activated platelets can mediate the onset of hypercoagulability in cancer patients by interacting with other blood cells. First, the interaction of platelets with leukocytes is likely involved in inducing a procoagulant state in cancer patients. In an

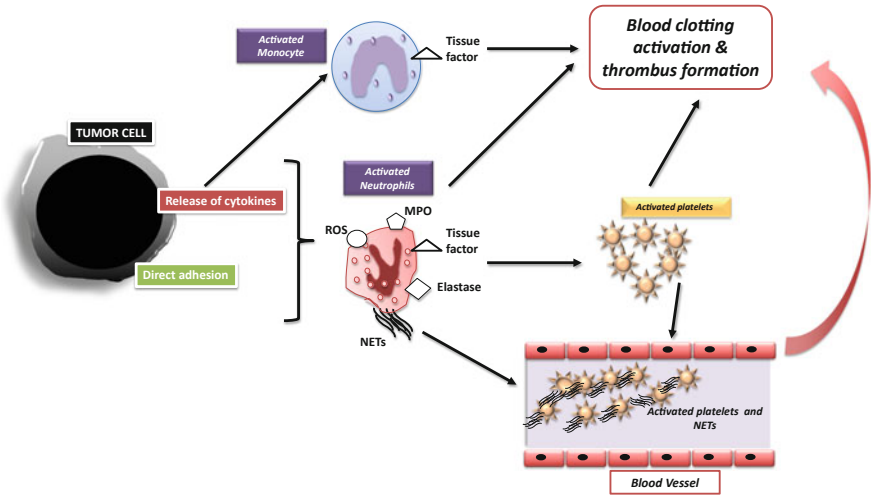

Fig. 2.4 Leukocytes' procoagulant activities elicited by tumor cells. The subpopulations of leukocytes involved in the clotting activation in cancer patients are neutrophils and monocytes. Tumor cells can activate leukocytes by direct cell–cell adhesion or by the release of cytokines and growth factors in the bloodstream. Neutrophils activated by tumor cells release procoagulant enzymes and expose on their surface high levels of TF, adhesion molecules for platelets and endothelial cells, and neutrophil extracellular traps (NETs), thus promoting the activation of blood clotting cascade. Moreover, activated platelets can provide signals that promote formation of NETs, which provide a scaffold and a stimulus for platelet adhesion and thrombus formation. Activated monocytes/macrophages express highly procoagulant TF and coagulation factors on their surface upon activation by cytokines, leading to fibrin formation and deposition

animal model of CAT, platelet–leukocyte interaction, as mediated by P-selectin on platelets and P-selectin glycoprotein ligand (PSLGI) on leukocytes, was necessary for the formation of mucin-induced lung microthrombi [110]. Moreover, platelets stimulate the release of neutrophil extracellular DNA traps (NETs) by leukocytes, which promote venous thrombosis (see Sect. 2.3.2.2). Second, the interaction of platelets with endothelial cells is relevant for platelet-mediated CAT. A study in a mouse model of deep vein thrombosis suggests that platelets have a critical role in thrombus formation in a condition of flow restriction, through the interaction with von Willebrand factor (vWF) bound to the endothelium [111]. Finally, platelets promote thrombosis in cancer patients by the activation of the coagulation cascade leading to thrombin generation. Indeed, activated platelet exposes phosphatidylserine (PS) on their outer membrane, which provides a negatively charged surface for initiation of fibrin clot formation [112]. Furthermore, adherent activated platelets release procoagulant PMPs, which further contribute to the fibrin deposition and microthrombi formation, as previously described (see Sect. 2.3.1.2).

2.3.2.2 Leukocytes Activation by Tumor Cells

Leukocyte numbers are frequently elevated in cancer patients, but also they circulate in an activated status as they are challenged by tumor cells to exhibit a procoagulant phenotype. The most important subpopulations of leukocytes involved in the clotting activation are **neutrophils** and **monocytes**. Tumor cells can activate leukocytes by direct cell–cell adhesion or by the release of cytokines and growth factors in the bloodstream (Fig. 2.4). In particular, G-CSF is produced by many tumors and is found elevated in the circulation of many cancer patients [13]. G-CSF increases the number of neutrophils and induces their activation.

Tumor-cell-activated neutrophils release procoagulant enzymes, including elastase and myeloperoxidase (MPO). They also expose on their surface high levels of TF and adhesion counter-receptors for platelet and endothelial cell adhesion molecules, as documented in myeloproliferative neoplasms [113, 114].

There is emerging evidence that cancer cells also predispose neutrophils to the release of DNA extracellular traps ("neutrophil extracellular traps" or NETs) [115]. NETs were first identified as a host defense mechanism against pathogens. They are the result of externalized DNA (nuclear or mitochondrial) released from the nucleus of neutrophils, decorated by histones and granular proteases following activation by bacterial LPS or cytokines. During sepsis, this mechanism named NETosis creates a high local concentration of proteases and provides a method of entrapment and killing of pathogens. However, NETs are also known to promote coagulation, providing a scaffold and a stimulus for platelet adhesion and thrombus formation [116]. The prothrombotic effect of NETs can be explained by their high content of negatively charged nucleic acids and histones, providing a strong activation signal for platelets, which translates into platelet aggregation and thrombosis [116]. At the same time, activated platelets can provide signals that promote formation of NETs [117]. In addition to its implication in thrombosis, the formation of NETs in cancer may affect the tumor biology. Tumor infiltrating-neutrophils can exert a role in promoting different steps of tumor progression. Of interest, the procoagulant activity of NETs leads to the generation of thrombin, which can affect all aspects of cancer progression [118].

The role of activated monocytes/macrophages in CAT is well known. Since the 80s, different studies have demonstrated that macrophages infiltrating the tumor are locally activated toward a procoagulant activity that contributes to fibrin deposition within malignant tissues [119, 120]. A study in ovarian cancer showed that in advanced disease, blood monocytes were activated to a procoagulant phenotype, adding to the activation of intravascular coagulation and thrombo-embolic complications [121]. Notably, monocytes are the only circulating blood cells that are able to synthetize and express highly procoagulant TF on their surface upon activation by cytokines (i.e., IL-lβ, TNF-α) and LPS [122]. Cancer cells can secrete these mediators, thus triggering the monocyte-induced mechanism of thrombosis. Moreover, macrophages infiltrating the tumor have been found to express coagulation factors II, V, VII, and X on their surface [122]. More recent studies have shown that blood monocytes are also capable to release extracellular traps (ETs) in response to several inflammatory stimuli. Monocyte ETs display a morphology

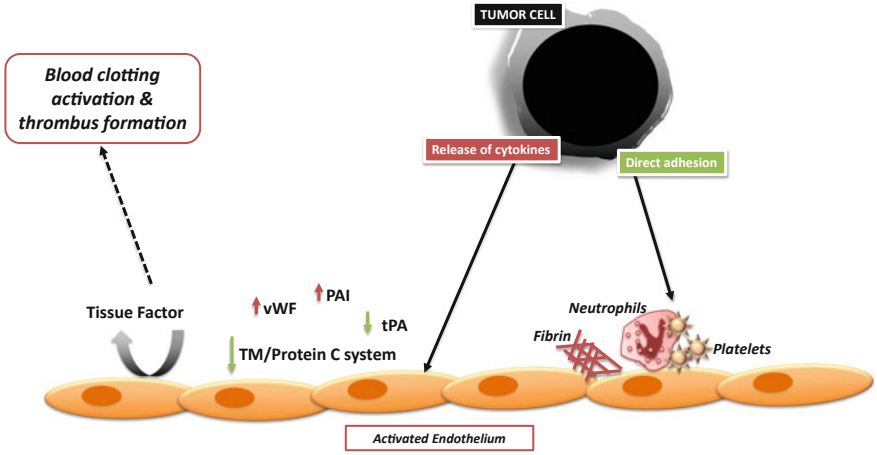

Fig. 2.5 Endothelium prothrombotic activation by cancer cells. Tumor cells can activate endothelial cells directly by cell–cell adhesion or by the release of proinflammatory cytokines. Cytokines regulate the expression of endothelial cell products active in hemostasis, including thrombomodulin (TM), TF, vWF, selectins, and fibrinolysis proteins (PAI-1)

similar to NETs, being associated to MPO, lactoferrin, citrullinated histones, and elastase, and a procoagulant activity [123]; however, their role in CAT needs to be further elucidated. Finally, a recent study in lung cancer patients with VTE found a relation between a high absolute monocyte count with a refractoriness to anticoagulant therapy and poor prognosis [124].

2.3.2.3 Endothelium Activation by Tumor Cells

Physiologically, the endothelium facilitates the blood flow by providing an antithrombotic surface that inhibits platelets' adhesion and coagulation activation. Several factors can perturb the resting state of endothelium in cancer patients (Fig. 2.5). Tumor cells can activate endothelial cells directly by cell–cell adhesion, as demonstrated in studies in non-small cell lung and colorectal carcinomas [125], or by the release of proinflammatory cytokines and acute phase proteins, which trigger the activation of endothelial cells as well as of monocytes [126]. In addition, in malignancy, reactive oxygen species and intracellular proteases released by activated neutrophils can induce detachment or lysis of endothelial cells, affecting functions involved in thrombomodulation.

Among cytokines, interleukin-lβ (IL-lβ) and tumor necrosis factor (TNF-α) can regulate the expression of endothelial cell products active in hemostasis, including thrombomodulin (TM), TF, vWF, adhesive receptors (i.e., selectins), and fibrinolysis proteins (i.e., fibrinolysis inhibitor PAI-1) [127]. TM is a membrane receptor of vascular endothelial cells with a potent anticoagulant function [128], since it binds and forms a complex with thrombin to activate the natural anticoagulant protein C. In cancer patients, increased levels of soluble TM and reduced expression of surface TM have been observed [129], leading to a loss of anticoagulant membrane TM at

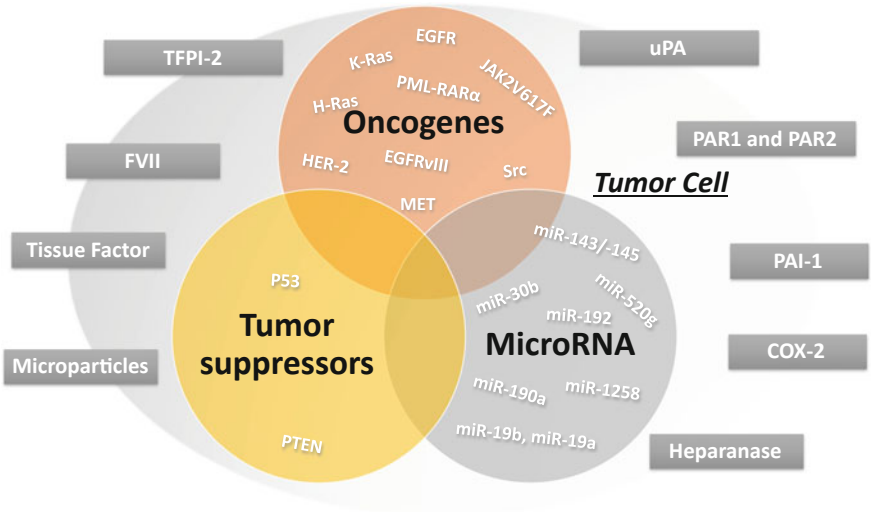

Fig. 2.6 Oncogenes, tumor suppressor genes, and microRNA implicated in hypercoagulability in cancer. Genes for neoplastic transformation also drive the programs for the expression of hemostatic proteins in cancer tissues

the endothelial outward. Furthermore, soluble TF released from endothelial cells in response to TNF-α has been demonstrated and is a marker of increased expression of TF on endothelial cells surface, a potent mechanism of prothrombotic response to inflammation [130]. Upregulation of the procoagulant TF with downregulation of the anticoagulant TM/protein C system converts the normal anticoagulant endothelium into a prothrombotic endothelium. Increased levels of vWF released from the endothelium are also described in cancer patients, and are of particular relevance in the pathogenesis of thrombosis in myeloproliferative neoplasms: Once platelets bind to vWF, they become activated and are able to aggregate and strengthen a clot [131]. Activated endothelium can also shed soluble adhesion molecules like selectins, which are commonly expressed by endothelial cells (P-selectin, E-selectin), platelets (P-selectin), and leukocytes (L-selectin). Increased levels of circulating E-selectin and P-selectin have been described in patients with myeloproliferative neoplasms and thrombosis [132], as well as in patients with lung and breast cancers [133, 134]. Moreover, reduced plasma levels of nitric oxide (NO) produced by endothelial cells, which inhibits platelet adhesion, activation, and aggregation, represent another mechanism of thrombus formation in myeloproliferative neoplasms [135]. Finally, circulating endothelial cells (CECs) have been established as markers of endothelial damage or dysfunction [136]. CEC levels increase in many types of solid tumors and hematological malignancies, and correlate with angiogenetic activity and tumor progression [137, 138], although their role in CAT has yet to be established.

2.4 The Oncogene Perspectives

In the last decade, molecular studies have demonstrated that oncogenes and repressor genes responsible for neoplastic transformation (i.e., mutation/induction of KRAS, EGFR, or MET, loss of PTEN, or TP53) also drive the programs for the expression of hemostatic proteins in cancer tissues (Fig. 2.6). Coagulopathy and thrombosis have been regarded for a long time as unspecific consequences of cancer-related disruption in tissue anatomy and vascular continuity, or driven by vascular hyperpermeability, inflammation, stasis, and toxic side effect [8]. Recent studies, however, suggest that activated coagulation may possess cancer-specific properties [8]. Rak and colleagues proposed that the type of cancer cell influenced the state of the coagulation system, as different cancers differ greatly in terms of risk of VTE [139]. Indeed, pancreatic, brain, gastrointestinal, ovarian, and hematological malignancies are all associated with a higher risk of VTE compared to skin, breast, and prostate cancer [26].

Specific genotypes of cancer cells may affect the coagulation system either directly or through changes in tumor environment [140]. For instance, it is documented that several dominant oncogenes, such as RAS, EGFRvIII, MET, and many other genetic lesions frequently upregulate VEGF, enhancing neo-angiogenesis [141]. Oncogenes' pathways also influence the recruitment of inflammatory cells, which themselves may exhibit proangiogenic and procoagulant phenotypes [142, 143]. However, oncogenic pathways also deregulate coagulation effectors more directly, through several different types of effects, i.e., by the abnormally high/constitutive expression of TF [144], by triggering the ectopic expression of coagulation genes [140, 145, 146], or by the emission of TF-bearing large and small microparticles that can enter biofluids and the general circulation [147]. In addition, mutations in different oncogenes and the loss of some repressor genes in different types of tumors may activate the coagulation system using one or another of these mechanisms. For example, in colorectal cancer, mutant KRAS is able to upregulate the expression of TF-bearing MPs; nonetheless, in the same type of cells the deletion of TP53 has been associated to enhanced TF exposure and shedding [36]. Overexpression of EGFR and HER-2, both upstream activators of the RAS signaling cascade, resulted in increased TF production in glioma and carcinoma cells, respectively [77, 146]. TF may also be upregulated by the mutation of the oncogene MET in hepatoma [148] and by the loss of PTEN tumor suppressor, especially under hypoxia, in glioblastoma [149]. Finally, several types of microRNA (miRNA) have been implicated in alterations of coagulant properties of cancer cells (i.e., expression and regulation of TF, heparanase, PAR-1, PAI-1, and COX-2) [150–154].

Genetic regulation of coagulation factors in cancer cells implies that molecularly different subtypes of cancer should exhibit different coagulation patterns (or "coagulomes"). Indeed, molecular profiling of human glioblastoma (GBM) has recently revolutionized the classification of this malignancy in four molecular subgroups, which effectively constitute different disease entities but also display a

different pattern of activation of the coagulation system [108, 140]. These data suggest that activation of oncogenic pathways contributes to both quantitative and qualitative rearrangements of the cellular "coagulome," which seems to be specific for each tumor type. It may also be possible that in different patients, even if affected by the same disease, thrombosis could be triggered by somewhat different mechanisms and could, hypothetically, be opposed using approaches based on the "coagulome" of the underlying disease. Thus, the coagulant phenotype of cancer cells could be viewed as one of several important effector mechanisms that link genetic progression of the disease and its biological and clinical behavior [8]. This does not necessarily imply a direct proportionality between procoagulant properties and clinical aggressiveness, but suggests that deregulation of hemostatic proteins may influence the tumor microenvironment in pathogenically significant ways. Some authors have also postulated that the coagulation system could play a role at preclinical, or otherwise occult stage of malignancy, and in particular that thrombin might trigger the growth of dormant cancer cells [155]. Dormant cells could be awakened by tissue injury, cardiovascular disease, or other conditions that may activate the clotting system. In this regard, interestingly, a higher frequency of colorectal cancer was recently described in certain forms of thrombophilia, especially in association with the homozygous mutation of the factor V Leiden [156]. Importantly, a recent study has demonstrated that in glioblastoma, exogenous expression of TF disrupts the dormant state of transformed but indolent tumor cells, both by recruitment of inflammatory cells and blood vessels and by facilitating gene mutations and silencing [38].

All these evidences contribute to postulate that procoagulant events are probably not an accompanying phenomenon in cancer, but an effector in tumor growth and progression, and possibly an initiator of malignant transformation. For instance, it is arguable that a better control of hemostatic perturbations may offer new means of therapy, control, and prevention in cancer.

2.5 Conclusions

Cancer-associated thrombosis is a major clinical issue, since thrombotic events increase morbidity and mortality of cancer patients. There is now growing knowledge about the mechanisms of hypercoagulability which predisposes to thrombotic complications, and this does not only translate into a better understanding of the pathogenesis but also offers new potential therapeutic targets of cancer-associated thrombosis. A very important advance in our knowledge has been the discovery that these cellular events can be genetically driven, involving the same genes driving tumorigenesis, as a mechanism of tumor growing and survival. Thus, targeting the mechanisms of coagulation activation could be beneficial for the treatment of the tumor itself. Finally, the biological markers of activation of the clotting system can be a clinical tool, which will help to identify the subgroups of

patients at higher risk of VTE and to establish more accurate and targeted anticoagulation strategies to prevent thrombosis in cancer patients.

References

1. Falanga A, Marchetti M, Vignoli A (2013) Coagulation and cancer: biological and clinical aspects. J Thromb Haemost 11:223–233
2. Lee AYY, Levine MN (2003) Venous thromboembolism and cancer: risks and outcomes. Circulation 107(Suppl 23)
3. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC (2013) Epidemiology of venous thrombosis. Blood 122(10):1712–1723
4. Blom JW, Vanderschoot JPM, Oostindiër MJ, Osanto S, van der Meer FJM, Rosendaal FR (2006) Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: results of a record linkage study. J Thromb Haemost 4(3):529–535
5. Blom J, Doggen C, Osanto S, Rosendaal F (2005) Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA 9(293):715–722
6. Falanga A, Russo L (2012) Epidemiology, risk and outcomes of venous thromboembolism in cancer. Hamostaseologie 32:115–125
7. Falanga A, Russo L, Milesi V (2014) The coagulopathy of cancer. Curr Opin Hematol 21:423–429
8. Magnus N, D'Asti E, Meehan B, Garnier D, Rak J (2014) Oncogenes and the coagulation system—forces that modulate dormant and aggressive states in cancer. Thromb Res 133(Suppl 2):S1–S9
9. Khorana AA, McCrae KR (2014) Risk stratification strategies for cancer-associated thrombosis: an update. Thromb Res 133(Suppl 2):35–38
10. Falanga A, Marchetti M, Russo L (2015) The mechanisms of cancer-associated thrombosis. Thromb Res 135:S8–S11
11. Khorana AA, Francis CW, Culakova E, Lyman GH (2005) Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. Cancer 104(12): 2822–2829
12. Simanek R, Vormittag R, Ay C, Alguel G, Dunkler D, Schwarzinger I et al (2010) High platelet count associated with venous thromboembolism in cancer patients: results from the Vienna Cancer and Thrombosis Study (CATS). J Thromb Haemost 8(1):114–120
13. Demers M, Wagner DD (2003) Neutrophil extracellular traps: a new link to cancer-associated thrombosis and potential implications for tumor progression. Oncoimmunology 2(2)
14. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW (2008) Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 111(10): 4902–4907
15. Ay C, Dunkler D, Marosi C, Chiriac A-L, Vormittag R, Simanek R et al (2010) Prediction of venous thromboembolism in cancer patients. Blood 116(24):5377–5382
16. Moore RA, Adel N, Riedel E, Bhutani M, Feldman DR, Tabbara NE et al (2011) High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: A large retrospective analysis. J Clin Oncol 29(25):3466–3473
17. Menter DG, Tucker SC, Kopetz S, Sood AK, Crissman JD, Honn KV (2014) Platelets and cancer: a casual or causal relationship: Revisited. Cancer Metastasis Rev 33(1):231–269
18. Gran OV, Braekkan SK, Hansen JB (2018) Prothrombotic genotypes and risk of venous thromboembolism in cancer. Thromb Res
19. Rosendaal F (1999) Venous thrombosis: a multicausal disease. Lancet 353(9159): 1167–1173

20. Decousus H, Moulin N, Quenet S, Bost V, Rivron-Guillot K, Laporte S et al (2007) Thrombophilia and risk of venous thrombosis in patients with cancer. Thromb Res 120(Suppl 2):51–61
21. Pabinger I, Ay C, Dunkler D, Thaler J, Reitter EM, Marosi C et al (2015) Factor V Leiden mutation increases the risk for venous thromboembolism in cancer patients—results from the Vienna Cancer And Thrombosis Study (CATS). J Thromb Haemost 13(1):17–22
22. Gran OV, Smith EN, Brækkan SK, Jensvoll H, Solomon T, Hindberg K et al (2016) Joint effects of cancer and variants in the factor 5 gene on the risk of venous thromboembolism. Haematologica 101(9):1046–1053
23. Dentali F, Gianni M, Agnelli G, Ageno W (2007) Association between inherited thrombophilic abnormalities and central venous catheter thrombosis in patients with cancer: results of the CAVECCAS study. J Thromb Haemost 6:70–75
24. Jick H, Slone D, Westerholm B, Inman W, Vessey M, Shapiro S et al (1969) Venous thromboembolic disease and ABO blood type. A cooperative study. Lancet 15(1):539–542
25. Sode BF, Allin KH, Dahl M, Gyntelberg F, Nordestgaard BG (2013) Risk of venous thromboembolism and myocardial infarction associated with factor V Leiden and prothrombin mutations and blood type. CMAJ 185(5):E229–E237
26. Wun T, White RH (2009) Epidemiology of cancer-related venous thromboembolism. Best Pr Res Clin Haematol 22(1):9–23
27. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH (2007) Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. Cancer 110(10):2339–2346
28. Falanga A, Marchetti M (2012) Anticancer treatment and thrombosis. Thromb Res 129(3): 353–359
29. Lechner D, Weltermann A (2008) Chemotherapy-induced thrombosis: a role for microparticles and tissue factor? Semin Thromb Hemost 34(2):199–203
30. Kakkar A, Lemoine N, Scully M, Tebbutt S, Williamson R (1995) Tissue factor expression correlates with histological grade in human pancreatic cancer. Br J Surg 82(8):1101–1104
31. Hamada K, Kuratsu J, Saitoh Y, Takeshima H, Nishi T, Ushio Y (1996) Expression of tissue factor correlates with grade of malignancy in human glioma. Cancer 77:1877–1883
32. Takano S, Tsuboi K, Tomono Y, Mitsui Y, Nose T (2000) Tissue factor, osteopontin, alphavbeta3 integrin expression in microvasculature of gliomas associated with vascular endothelial growth factor expression. Br J Cancer 82(12):1967–1973
33. Guan M, Jin J, Su B, Liu W, Lu Y (2002) Tissue factor expression and angiogenesis in human glioma. Clin Biochem 35(4):321–325
34. Ishimaru K, Hirano H, Yamahata H, Takeshima H, Niiro M, Kuratsu J (2003) The expression of tissue factor correlates with proliferative ability in meningioma. Oncol Rep 10:1133–1137
35. Fernandes RS, Kirszbeg C, Rumjanek M, Monteiro RQ (2006) On the molecular mechanisms for the highly procoagulant pattern of C6 glioma cells. J Thromb Haemost 4:1546–1552
36. Yu JL, May L, Lhotak V, Shahrzad S, Shirasawa S, Weitz JI et al (2005) Oncogenic events regulate tissue factor expression in colorectal cancer cells: implications for tumor progression and angiogenesis. Blood 105(4):1734–1742
37. Davila M, Amirkhosravi A, Coll E, Desai H, Robles L, Colon J et al (2008) Tissue factor-bearing microparticles derived from tumor cells: impact on coagulation activation. J Thromb Haemost 6:1517–1524
38. Magnus N, Garnier D, Meehan B, Mcgraw S, Hoon T, Caron M (2014) Tissue factor expression provokes escape from tumor dormancy and leads to genomic alterations. PNAS 111(9):3544–3549
39. Falanga A, Russo L, Milesi V, Vignoli A (2017) Mechanisms and risk factors of thrombosis in cancer. Crit Rev Oncol Hematol 118:79–83

40. Falanga A, Consonni R, Marchetti M, Locatelli G, Garattini E, Gambacorti Passerini C et al (1998) Cancer procoagulant and tissue factor are differently modulated by all-trans-retinoic acid in acute promyelocytic leukemia cells. Blood 92(1):143–151
41. Falanga A, Iacoviello L, Evangelista V, Belotti D, Consonni R, D'Orazio A et al (1995) Loss of blast cell procoagulant activity and improvement of hemostatic variables in patients with acute promyelocytic leukemia administered all-trans-retinoic acid. Blood 86(3):1072–1081
42. Falanga A, Toma S, Marchetti M, Palumbo R, Raffo P, Consonni R et al (2002) Effect of all-trans-retinoic acid on the hypercoagulable state of patients with breast cancer. Am J Hematol 70:9–15
43. Nadir Y, Brenner B (2014) Heparanase multiple effects in cancer. Thromb Res. Elsevier Masson SAS 133:S90–S94
44. Xu X, Quiros RM, Maxhimer JB, Jiang P, Marcinek R, Ain KB et al (2003) Inverse correlation between heparan sulfate composition and heparanase-1 gene expression in thyroid papillary carcinomas: a potential role in tumor metastasis. Clin Cancer Res 9:5968–5979
45. El-assal ON, Yamanoi A, Ono T, Kohno H, Nagasue N (2001) The clinicopathological significance of heparanase and basic fibroblast growth factor expressions in hepatocellular carcinoma. Clin Cancer Res 7(May):1299–1305
46. Folkman J, Klagsbrun M, Sasse J, Wadzinski M, Ingber D, Vlodavsky I (1988) A heparin-binding angiogenic protein-basic fibroblast growth factor is stored within basement membrane. Am J Pathol 130(2):393–400
47. Vlodavsky I, Folkmantt J, Sullivant R, Fridman R, Ishai-michaeli R, Sasset J et al (1987) Endothelial cell-derived basic fibroblast growth factor: synthesis and deposition into subendothelial extracellular matrix. Proc Nati Acad Sci USA 84(April):2292–2296
48. Friedmann Y, Vlodavsky I, Aingorn H, Aviv A, Peretz T, Pecker I, et al (2000) Expression of heparanase in normal, dysplastic, and neoplastic human colonic mucosa and stroma. evidence for its role in colonic tumorigenesis. Am J Pathol 157(4):1167–1175
49. Elkin M, Ilan N, Ishai-Michaeli R, Friedmann Y, Papo O, Pecker I et al (2001) Heparanase as mediator of angiogenesis: mode of action. FASEB J 15(9):1661–1663
50. Nadir Y, Brenner B (2016) Heparanase procoagulant activity in cancer progression. Thromb Res 140:S44–S48
51. Ahn YS (2005) Cell-derived microparticles: "Miniature envoys with many faces". J Thromb Haemost 3:884–887
52. Horstman LL, Jy W, Jimenez JJ, Bidot C, Ahn YS (2004) New horizons in the analysis of circulating cell-derived microparticles. Keio J Med 53(4):210–230
53. Nomura S, Suzuki M, Katsura K, Xie GL, Miyazaki Y, Miyake T et al (1995) Platelet-derived microparticles may influence the development of atherosclerosis in diabetes mellitus. Atherosclerosis 116:235–240
54. Mallat Z, Benamer H (2000) Elevated levels of shed membrane microparticles with procoagulant potential in the peripheral circulating blood. Circulation 101:841–843
55. Nieuwland R, Berckmans J, Mcgregor S, Bo AN, Romijn FPHTM, Westendorp RGJ, et al (2000) Cellular origin and procoagulant properties of microparticles in meningococcal sepsis. Blood 95(3):930–936
56. Chirinos JA, Heresi GA, Velasquez H, Jy W, Jimenez JJ, Ahn E, et al (2005) Elevation of endothelial microparticles, platelets, and leukocyte activation in patients with venous thromboembolism. J Am Coll Cardiol. Elsevier Masson SAS 45(9):1467–1471
57. Piccioli A, Falanga A, Baccaglini U, Marchetti M, Prandoni P (2006) Cancer and venous thromboembolism. Semin Thromb Hemost 32(7):694–699
58. Falanga A, Marchetti M (2009) Venous thromboembolism in the hematologic malignancies. J Clin Oncol 27(29):4848–4857
59. Kim H, Song K, Park Y, Kang Y, Lee Y, Lee K et al (2003) Elevated levels of circulating platelet microparticles, VEGF, IL-6 and RANTES in patients with gastric cancer: possible role of a metastasis predictor. Eur J Cancer 39(2):184–191

60. Del Conde I, Bharwani LD, Dietzen DJ, Pendurthi U, Thiagarajan P, LóPez JA (2007) Microvesicle-associated tissue factor and Trousseau's syndrome. J Thromb Haemost 5(1):70–74
61. Tilley RE, Holscher T, Belani R, Nieva J, Mackman J (2008) Tissue factor activity is increased in a combined platelet and microparticle sample from cancer patients. Thromb Res 122(5):604–609
62. Falanga A, Barbui T, Rickles FR (2008) Hypercoagulability and tissue factor gene upregulation in hematologic malignancies. Semin Thromb Hemost 34(2):204–210
63. Dvorak HF, Quay SC, Orenstein NS, Dvorak AM, Hahn P, Bitzer AM, et al (1981) Tumor shedding and coagulation. Science 212(4497):923–924
64. Bastida E, Ordinas A, Escolar G, Jamieson GA (1984) Tissue factor in microvescicles shed from U87MG human glioblastoma cells induces coagulation, platelet aggregation, and thrombogenesis. Blood 64(1):177–184
65. Yu JL, Rak JW (2004) Shedding of tissue factor (TF)-containing microparticles rather than alternatively spliced TF is the main source of TF activity released from human cancer cells. J Thromb Haemost 2(11):2065–2067
66. Tesselaar MET, Romijn FPHTM, Van Der Linden IK, Prins FA, Bertina RM, Osanto S (2006) Microparticle-associated tissue factor activity: a link between cancer and thrombosis? J Thromb Haemost 5:520–527
67. Manly DA, Wang J, Glover SL, Kasthuri R, Liebman HA, Key S et al (2010) Increased microparticle tissue factor activity in cancer patients with venous thromboembolism. Thromb Res 125(6):511–512
68. Kwaan HC, Magalha E (2010) Role of microparticles in the hemostatic dysfunction in acute promyelocytic leukemia. Semin Thromb Hemost 36(8):917–924
69. van Aalderen MC, Trappenburg MC, van Schilfgaarde M, Molenaar PJ (2011) Procoagulant myeloblast-derived microparticles in AML patients: changes in numbers and thrombin generation potential during chemotherapy. J Thromb Haemost 9:223–234
70. Auwerda JJ, Yuana Y, Osanto S, de Maat MP, Sonneveld P, Bertina RM et al (2011) Microparticle-associated tissue factor activity and venous thrombosis in multiple myeloma. Thromb Haemost 105(1):14–20
71. Trappenburg MC, Van Schilfgaarde M, Marchetti M, Spronk HM, Cate H, Leyte A et al (2009) Elevated procoagulant microparticles expressing endothelial and platelet markers in essential thrombocythemia. Haematologica 94(7):911–998
72. Martinez MC, Andriantsitohaina R (2011) Microparticles in angiogenesis: therapeutic potential. Circ Res 109:110–119
73. Kim HK, Song KS, Chung J, Lee KR, Lee S (2004) Platelet microparticles induce angiogenesis in vitro. Br J Haematol 124:376–384
74. Janowska-wieczorek A, Wysoczynski M, Kijowski J, Marquez-curtis L, Machalinski B, Ratajczak J et al (2004) Microvesicles derived from activated platelets induce metastasis and angiogenesis in lung cancer. Int J Cancer 113:752–760
75. Falanga A, Marchetti M, Vignoli A, Balducci D (2003) Clotting mechanisms and cancer: implications in thrombus formation and tumor progression. Clin Adv Hematol Oncol 1(11): 673–678
76. Ruf W, Yokota N, Schaffner F (2010) Tissue factor in cancer progression and angiogenesis. Thromb Res 2018(125):S36–S38
77. Milsom CC, Yu JL, Mackman N, Micallef J, Anderson GM, Guha A et al (2008) Tissue factor regulation by epidermal growth factor receptor and epithelial-to-mesenchymal transitions: effect on tumor initiation and angiogenesis. Cancer Res 68(24):10068–10077
78. Zwicker JI (2010) Predictive value of tissue factor bearing microparticles in cancer associated thrombosis. Thromb Res. Elsevier Ltd 125:S89–S91
79. Erdmann D, Heim J (1995) Orphan nuclear receptor HNF-4 binds to the human coagulation factor VII promoter. J Biol Chem 270(39):22988–22996

80. Tsao BYBP, Fair DS, Curtiss LK, Edgington TS (1984) Monocytes can be induced by lipopolysaccharide-triggered T lymphocytes to express functional factor VII/VIIa protease activity. J Exp Med 159:1042–1057
81. Chapman HA Jr, Allen CL, Stone OL, Fair DS. Human alveolar macrophages synthesize factor VII in vitro. Possible role in interstitial lung disease. J Clin Invest 75:2030–2037
82. Neaud V, Hisaka T, Monvoisin A, Bedin C, Balabaud C, Foster DC et al (2000) Paradoxical pro-invasive effect of the serine proteinase inhibitor tissue factor pathway inhibitor-2 on human hepatocellular carcinoma cells. J Biol Chem 275(45):35565–35569
83. Fischer EG, Riewald M, Huang HY, Miyagi Y, Kubota Y, Mueller BM et al (1999) Tumor cell adhesion and migration supported by interaction of a receptor-protease complex with its inhibitor. J Clin Invest 104(9):1213–1221
84. Zacharski LR, Memoli VA, Ornstein DL, Rousseau SM, Kisiel W, Kudryk BJ (1993) Tumor cell procoagulant and urokinase expression in carcinoma of the ovary. J Natl Cancer Inst 85 (15):1225–1230
85. Wojtukiewicz MZ, Zacharski LR, Ruciñska M, Zimnoch L, Jaromin J, Rózañska-Kudelska M, et al (1999) Expression of tissue factor and tissue factor pathway inhibitor in situ in laryngeal carcinoma. Thromb Haemost 82:1659–1662
86. Koizume S, Jin M-S, Miyagi E, Hirahara F, Nakamura Y, Piao J-H et al (2006) Activation of cancer cell migration and invasion by ectopic synthesis of coagulation factor VII. Cancer Res 66(19):9453–9460
87. Tang J, Fan Q, Wu W, Jia Z, Li H, Yang Y et al (2010) Extrahepatic synthesis of coagulation factor VII by colorectal cancer cells promotes tumor invasion and metastasis. Chin Med J 123(24):3559–3565
88. Yokota N, Koizume S, Miyagi E, Hirahara F, Nakamura Y, Kikuchi K et al (2009) Self-production of tissue factor-coagulation factor VII complex by ovarian cancer cells. Br J Cancer 101(12):2023–2029
89. Kyrle PA, Minar E, Hirschl M, Bialonczyk C, Stain M, Schneider B et al (2000) High plasma levels of factor VIII and the Risk of recurrent venous thromboembolism. N Engl J Med 343(7):457–462
90. Legnani C, Cosmi B, Cini M, Frascaro M, Giuliana G, Palareti G (2004) High plasma levels of factor VIII and risk of recurrence of venous thromboembolism. Br J Haematol 124(4): 504–510
91. Auwerda JJA, Sonneveld P, De Maat MPM, Leebeek FWG (2007) Prothrombotic coagulation abnormalities in patients with newly diagnosed multiple myeloma. Haematologica 92(2):279–280
92. Yigit E, Gönüllü G, Yücel I, Turgut M, Erdem D, Çakar B (2008) Relation between hemostatic parameters and prognostic/predictive factors in breast cancer. Eur J Intern Med 19(8):602–607
93. Battistelli S, Stefanoni M, Lorenzi B, Dell'Avanzato R, Varrone F, Pascucci A et al (2008) Coagulation factor levels in non-metastatic colorectal cancer patients. Int J Biol Markers 23(1):36–41
94. Dogan M, Demirkazik A, Konuk N, Yalcin, Buyukcelik A, Utkan G, et al (2006) The effect of venous thromboembolism on survival of cancer patients and its relationship with serum level of factor VIII and vascular endothelial growth factor: a prospective matched-paired study. Int J Biol Markers 21(4):206–210
95. Vormittag R, Simanek R, Ay C, Dunkler D, Quehenberger P, Marosi C et al (2009) High factor VIII levels independently predict venous thromboembolism in cancer patients: The cancer and thrombosis study. Arterioscler Thromb Vasc Biol 29(12):2176–2181
96. Andrén-Sandberg A, Lecander I, Martinsson G, Astedt B (1992) Peaks in plasma plasminogen activator inhibitor-1 concentration may explain thrombotic events in cases of pancreatic carcinoma. Cancer 69(12):2884–2887

97. Sciacca FL, Ciusani E, Silvani A, Corsini E, Frigerio S, Pogliani S et al (2004) Genetic and plasma markers of venous thromboembolism in patients with high grade glioma. Clin Cancer Res 10(4):1312–1317
98. Chen N, Ren M, Li R, Deng X, Li Y, Yan K et al (2015) Bevacizumab promotes venous thromboembolism through the induction of PAI-1 in a mouse xenograft model of human lung carcinoma. Mol Cancer 14(1):1–7
99. Liu Y, Wang Z, Jiang M, Dai L, Zhang W, Wu D et al (2011) The expression of annexin II and its role in the fibrinolytic activity in acute promyelocytic leukemia. Leuk Res 35(7): 879–884
100. Connolly GC, Phipps RP, Francis CW (2014) Platelets and cancer-associated thrombosis. Semin Oncol. Elsevier 41(3):302–310
101. Falanga A, Russo L, Verzeroli C (2013) Mechanisms of thrombosis in cancer. Thromb Res. Elsevier Ltd 131:S59–S62
102. Lee EC, Cameron SJ (2017) Cancer and thrombotic risk: the platelet paradigm. Front Cardiovasc Med. 4(November):1–6
103. Läubli H, Borsig L (2010) Selectins promote tumor metastasis. Semin Cancer Biol 20 (3):169–177
104. Chen M, Geng JG (2006) P-selectin mediates adhesion of leukocytes, platelets, and cancer cells in inflammation, thrombosis, and cancer growth and metastasis. Arch Immunol Ther Exp (Warsz) 54(2):75–84
105. Stegner D, Dütting S, Nieswandt B (2014) Mechanistic explanation for platelet contribution to cancer metastasis. Thromb Res 133(Suppl 2):149–157
106. Palumbo JS, Talmage KE, Massari JV, La Jeunesse CM, Flick MJ, Kombrinck KW (2005) Platelets and fibrin (ogen) increase metastatic potential by impeding natural killer cell—mediated elimination of tumor cells. Blood J 105(1):178–185
107. Raica M, Cimpean AM, Ribatti D (2008) The role of podoplanin in tumor progression and metastasis. Anticancer Res 28(5B):2997–3006
108. Riedl J, Preusser M, Nazari PMS, Posch F, Panzer S, Marosi C et al (2017) Podoplanin expression in primary brain tumors induces platelet aggregation and increases risk of venous thromboembolism. Blood 129(13):1831–1839
109. Chang Y-W, Hsieh P, Chang Y, Lu M, Huang T-F, Chong K-Y et al (2015) Identification of a novel platelet antagonist that binds to CLEC-2 and suppresses podoplanin-induced platelet aggregation and cancer metastasis. Oncotarget 6(40):42733–42748
110. Shao B, Wahrenbrock MG, Yao L, David T, Coughlin SR, Xia L et al (2011) Carcinoma mucins trigger reciprocal activation of platelets and neutrophils in a murine model of Trousseau syndrome. Blood 118(15):4015–4023
111. Brill A, Fuchs T a, Chauhan AK, Yang JJ, Meyer SF De, Ko M, et al (2011) von Willebrand factor—mediated platelet adhesion is critical for deep vein thrombosis in mouse models. Blood 117(4):1400–1407
112. Vanschoonbeek K, Feijge MAH, Van Kampen RJW, Kenis H, Hemker HC, Giesen PLA et al (2004) Initiating and potentiating role of platelets in tissue factor-induced thrombin generation in the presence of plasma: Subject-dependent variation in thrombogram characteristics. J Thromb Haemost 2(3):476–484
113. Falanga A, Marchetti M, Evangelista V, Vignoli A, Licini M, Balicco M et al (2000) Polymorphonuclear leukocyte activation and hemostasis in patients with essential thrombocythemia and polycythemia vera. Blood 96(13):4261–4266
114. Barbui T, Finazzi G, Falanga A (2013) Myeloproliferative neoplasms and thrombosis. Blood 122(13):2176–2184
115. Demers M, Krause DS, Schatzberg D, Martinod K, Voorhees JR, Fuchs TA, et al (2012) Cancers predispose neutrophils to release extracellular DNA traps that contribute to cancer-associated thrombosis. Proc Natl Acad Sci USA 109(32):13076–13081

116. Fuchs TA, Brill A, Duerschmied D, Schatzberg D, Monestier M, Myers DD et al (2010) Extracellular DNA traps promote thrombosis. Proc Natl Acad Sci USA 107(36):15880–15885
117. Clark S, Ma A, Tavener S, McDonald B, Goodarzi Z, Kelly M et al (2007) Platelet TLR4 activates neutrophil extracellular traps to ensnare bacteria in septic blood. Nat Med 13(4): 463–469
118. Snyder KM, Kessler CM (2008) The pivotal role of thrombin in cancer biology and tumorigenesis. Semin Thromb Hemost 34(8):734–741
119. Edwards R, Rickles F (1984) Macrophage procoagulants. Prog Hemost Thromb 7:183–209
120. Semeraro N (1988) Different expression of procoagulant activity in macrophages associated with experimental and human tumors. Haemostasis 18:47–54
121. Semeraro N, Montemurro P, Conese M, Giordano D, Stella M, Restaino A et al (1990) Procoagulant activity of mononuclear phagocytes from different anatomical sites in patients with gynecological malignancies. Int J Cancer 45(2):251–254
122. Pabinger I, Posch F (2014) Flamethrowers: blood cells and cancer thrombosis risk. Hematol Am Soc Hematol Educ Program 2014 2014(1):410–417
123. Granger V, Faille D, Marani V, Noël B, Gallais Y, Szely N et al (2017) Human blood monocytes are able to form extracellular traps. J Leukoc Biol 102(3):775–781
124. Go S, Kim R, Song H, Kang M, Lee U, Choi H et al (2015) Prognostic significance of the absolute monocyte counts in lung cancer patients with venous thromboembolism. Tumour Biol 36(10):7631–7639
125. Tas F, Duranyildiz D, Argon A, Og H (2005) Serum levels of leptin and proinflammatory cytokines in advanced-stage non-small cell lung cancer. Med Oncol 22(4):353–354
126. Zwicker JI, Furie BC, Furie B (2007) Cancer-associated thrombosis. Crit Rev Oncol Hematol 62:126–136
127. Falanga A, Marchetti M, Giovanelli S, Barbui T (1996) All-trans-retinoic acid counteracts endothelial cell procoagulant activity induced by a human promyelocytic leukemia-derived cell line (NB4). Blood 87(2):613–618
128. Van de Wouwer M, Collen D, Conway EM (2004) Thrombomodulin-protein C-EPCR system: integrated to regulate coagulation and inflammation. Arterioscler Thromb Vasc Biol 24(8):1374–1383
129. Lindahl AK, Boffa MC, Abildgaard U (1993) Increased plasma thrombomodulin in cancer patients. Thromb Haemost 69(2):112–114
130. Szotowski B, Antoniak S, Poller W, Schultheiss HP, Rauch U (2005) Procoagulant soluble tissue factor is released from endothelial cells in response to inflammatory cytokines. Circ Res 96(12):1233–1239
131. Friedenberg WR, Roberts RC, Alonso-Escolano D (1992) Relationship of thrombohemorrhagic complications to endothelial cell function in patients with chronic myeloproliferative. Am J Hematol 40(4):283–289
132. Karakantza M, Giannakoulas NC, Zikos P, Sakellaropoulos G, Kouraklis A, Aktypi A et al (2004) Markers of endothelial and in vivo platelet activation in patients with essential thrombocythemia and polycythemia vera. Int J Hematol 79(3):253–259
133. Gogali A, Charalabopoulos K, Zampira I, Konstantinidis AK, Tachmazoglou F, Daskalopoulos G et al (2010) Soluble adhesion molecules E-cadherin, intercellular adhesion molecule-1, and E-selectin as lung cancer biomarkers. Chest 138(5):1173–1179
134. Silva HC, Garcao F, Coutinho EG, De Oliveira CF, Regateiro FJ (2006) Soluble VCAM-1 and E-selectin in breast cancer: relationship with staging and with the detection of circulating cancer cells. Neoplasma. 53(6):538–543
135. Cella G, Marchetti M, Vianello F, Panova-Noeva M, Vignoli A, Russo L et al (2010) Nitric oxide derivatives and soluble plasma selectins in patients with myeloproliferative neoplasms. Thromb Haemost 104(1):151–156

136. Goon PKY, Lip GYH, Boos CJ, Stonelake PS, Blann AD (2006) Circulating endothelial cells, endothelial progenitor cells, and endothelial microparticles in cancer. Neoplasia 8(2):79–88
137. Mancuso P, Burlini A, Pruneri G, Goldhirsch A, Martinelli G, Bertolini F (2001) Resting and activated endothelial cells are increased in the peripheral blood of cancer patients. Blood 97(11):3658–3662
138. Fleitas T, Martínez-Sales V, Vila V, Reganon E, Mesado D, Martín M et al (2012) Circulating endothelial cells and microparticles as prognostic markers in advanced non-small cell lung cancer. PLoS ONE 7(10):1–6
139. Rak J, Klement G (2000) Impact of oncogenes and tumor suppressor genes on deregulation of hemostasis and angiogenesis in cancer. Cancer Metastasis Rev 19(1–2):93–96
140. Magnus N, Gerges N, Jabado N, Rak J (2013) Coagulation-related gene expression profile in glioblastoma is defined by molecular disease subtype. J Thromb Haemost 11(6):1197–1200
141. Rak J, Mitsuhashi Y, Bayko L, Filmus J, Shirasawa S, Sasazuki T et al (1995) Advances in brief mutant ras oncogenes upregulate VEGFIVPF expression: implications for induction and inhibition of tumor angiogenesis. Cancer Res 55:4575–4580
142. Sparmann A, Bar-Sagi D (2004) Ras-induced interleukin-8 expression plays a critical role in tumor growth and angiogenesis. Cancer Cell 6(5):447–458
143. Phan VT, Wu X, Cheng JH, Sheng RX, Chung AS, Zhuang G et al (2013) Oncogenic RAS pathway activation promotes resistance to anti-VEGF therapy through G-CSF-induced neutrophil recruitment. Proc Natl Acad Sci USA 110(15):6079–6084
144. Rickles FR (2009) Cancer and thrombosis in women—molecular mechanisms. Thromb Res 123(Suppl 2):16–20
145. Koizume S, Yokota N, Miyagi E, Hirahara F, Nakamura Y, Sakuma Y et al (2009) Hepatocyte nuclear factor-4-independent synthesis of coagulation factor VII in breast cancer cells and its inhibition by targeting selective histone acetyltransferases. Mol Cancer Res 7 (12):1928–1936
146. Magnus N, Garnier D, Rak J (2010) Oncogenic epidermal growth factor receptor up-regulates multiple elements of the tissue factor signaling pathway in human glioma cells sure to FVIIa and PAR1- or PAR2-activat-. Blood 116(5):815–819
147. Garnier D, Magnus N, Lee TH, Bentley V, Meehan B, Milsom C et al (2012) Cancer cells induced to express mesenchymal phenotype release exosome-like extracellular vesicles carrying tissue factor. J Biol Chem 287(52):43565–43572
148. Provençal M, Berger-Thibaul N, Labbé D, Veitch R, Boivin D, Rivard G et al (2010) Tissue factor mediates the HGF/Met-induced anti-apoptotic pathway in DAOY medulloblastoma cells. J Neurooncol 97(3):365–372
149. Rong Y, Belozerov VE, Tucker-Burden C, Chen G, Durden DL, Olson JJ et al (2009) Epidermal growth factor receptor and PTEN modulate tissue factor expression in glioblastoma through JunD/activator protein-1 transcriptional activity. Cancer Res 69 (6):2540–2549
150. Zhang L, Sullivan PS, Goodman JC, Gunaratne PH, Marchetti D (2011) MicroRNA-1258 suppresses breast cancer brain metastasis by targeting heparanase. Cancer Res 71(3): 645–654
151. Chu HW, Cheng CW, Chou WC, Hu LY, Wang HW, Hsiung CN et al (2014) A novel estrogen receptor-microRNA 190a-PAR-1-pathway regulates breast cancer progression, a finding initially suggested by genome-wide analysis of loci associated with lymph-node metastasis. Hum Mol Genet 23(2):355–367
152. Botla SK, Savant S, Jandaghi P, Bauer AS, Mucke O, Moskalev EA et al (2016) Early epigenetic downregulation of microRNA-192 expression promotes pancreatic cancer progression. Cancer Res 76(14):4149–4159
153. Wu X-L (2013) MicroRNA-143 suppresses gastric cancer cell growth and induces apoptosis by targeting COX-2. World J Gastroenterol 19(43):7758

154. D'Asti E, Rak J (2016) Biological basis of personalized anticoagulation in cancer: oncogene and oncomir networks as putative regulators of coagulopathy. Thromb Res 140(Suppl 1): 37–43
155. Karpatkin S (2004) Does hypercoagulability awaken dormant tumor cells in the host? J Thromb Haemost 2(12):2103–2106
156. Vossen CY, Hoffmeister M, Chang-Claude JC, Rosendaal FR, Brenner H (2011) Clotting factor gene polymorphisms and colorectal cancer risk. J Clin Oncol 29(13):1722–1727

Pathophysiology 2: The Role of Platelets in Cancer Biology

3

Aime T. Franco and Jerry Ware

Contents

3.1 The History of Platelets and Cancer

The observation and naming of platelets in the bloodstream are credited to the Italian, Julius Bizzozero, in 1882. While others made reference to blood cells that were likely platelets, it was Bizzozero who suggested the platelet was unique among blood cells and participated in the arrest of blood flow. However, it was not until much later that the wound healing properties of a platelet were recognized

A. T. Franco (✉) · J. Ware
Department of Physiology & Biophysics, University of Arkansas for Medical Sciences, Slot 505, 4301 W. Markham Street, Little Rock, AR 72205, USA
e-mail: ATFranco@uams.edu

J. Ware
e-mail: Jware@uams.edu

G. Soff (ed.), *Thrombosis and Hemostasis in Cancer*, Cancer Treatment and Research 179, https://doi.org/10.1007/978-3-030-20315-3_3

[1, 2]. As the purveyor of the vasculature, an ability to prevent blood loss following injury and then create a local environment for wound healing and revascularization, the platelet is again ideally suited for contributing many aspects of the cancer process. As we shall illustrate, the platelet is well positioned to influence an even older cancer paradigm—"tumors: wounds that do not heal" [3, 4].

In the seminal 2000 "Hallmarks of Cancer," Hanahan and Weinberg provided a systematic dissection of the malignant process by identifying six characteristics that contribute to the progression of cancer [5]. Later, the hallmarks would be updated to include additional characteristics deemed to be necessary for malignant transformation and changes in the microenvironment [6]. Together, these landmark papers have provided a guide to the complex changes that occur during disease progression and dissemination, but more importantly have provided a step-by-step guide where the contribution of surrogate cancer participants, such as platelets, can be defined.

While the hemostatic attributes of circulating platelets date back to Bizzozero, their relevance in cancer biology was largely unappreciated and surrounded by skepticism [7]. As purveyors of vascular integrity, the platelet resides within the key conduit facilitating metastasis. Indeed, as others have recently pointed out, the bloodstream is considered a harsh environment for the tumor cell with only a minor fraction of cells capable of colonizing a distant metastatic site [8]. The platelet contribution to the metastatic process was recognized by Gasic et al. as an early milestone in the 1960s [9]. Soon thereafter, the same group provided a second milestone linking one of the most widely used antiplatelets or antithrombotic drugs, aspirin, to a reduction in metastasis [10]. Today, the molecular details of platelet involvement are being dissected in exquisite detail and extend beyond the metastatic process [7].

Here, we will integrate the older concepts of platelet physiology and tumor biology with the more recent state-of-the-art mechanistic studies linking the two. The beauty in the project is several folds: the mature understanding of platelet biology as it pertains to hemostasis and thrombosis, the availability of unique animal models, the available large datasets of patients receiving antiplatelet medication for cardiovascular disease, and the roadmap provided by the hallmarks of cancer. Thus, known platelet properties can be immediately added to the hallmarks filling important gaps in our understanding of cancer.

3.2 Platelet Structure/Function

Platelet function in hemostasis and thrombosis in its simplest form can be represented as a temporal sequence of events involving adhesion, activation, and aggregation to a damaged vascular surface. Major ligands supporting the adhesion and aggregation include collagen, von Willebrand factor (VWF), and fibrinogen. Highlighting the exquisite regulation of the platelet's role in hemostasis is the low

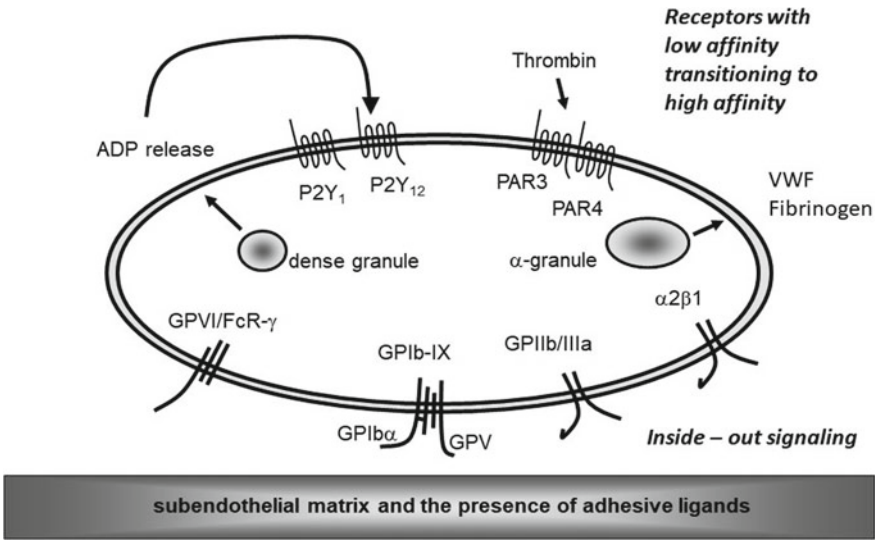

Fig. 3.1 Depicted is a simplified scheme of key receptors that support the platelet's role in hemostasis and thrombosis. The platelet paradigm involves the transition of the circulating unactivated platelet to an activated platelet releasing α-granule and dense granule components to support a platelet-rich thrombi. Among the important adhesion receptors are GPIb-IX, also referred to as GPIb-IX-V to include a fourth GPV gene product. GPIb-IX binds to surface-bound VWF, a key step in the initiation of thrombosis. Two platelet collagen receptors, GPVI/FcR-γ and α2β1, also support adhesion and generate activation signals to facilitate irreversible adhesion. Platelet activation involves stored granular components being released from structurally distinct dense and α-granules. Among the dense granule components released are ADP that activates platelets via the P2Y12 receptor. The P2Y12 receptor is clinically relevant as the target of multiple prodrug and drug therapies. A final step in activation transitions the integrin receptor, αIIβ3, from a receptor with a low affinity for fibrinogen to a high-affinity receptor capable of supporting interplatelet aggregation via fibrinogen

affinity between plasma VWF and fibrinogen as the platelet is circulating in blood. Yet, once the platelet recognizes surface-bound collagen or VWF, a plethora of intraplatelet and surface receptor changes are initiated. The molecular details of these processes have been widely described in detail [11]. Here, we focus on a few of the most physiologically relevant receptors and intraplatelet pathways, in particular focusing on those recognized as targets for antiplatelet therapy, acknowledging where there might be efficacy in cancer treatment or a better appreciation for mechanisms linked to cancer biology (summarized in Fig. 3.1) [12].

Adhesion—While the repertoire of surface membrane receptors on the platelet is quite extensive, three different complexes have been shown to significantly contribute to normal platelet physiology, glycoprotein (GP)Ib-IX, GPVI, and GPIIb/IIIa (αIIbβ3). From the adhesion standpoint, we focus on GPIb-IX and GPVI and their key interactions with VWF and collagen, respectively.

Human deficiencies of platelet GPIb-IX, (the Bernard–Soulier syndrome), or the GPIb-IX ligand (VWF)—both result in bleeding phenotypes. The Bernard–Soulier syndrome is a rare autosomal recessive disorder but associated with often life-threatening bleeding. The absence or expression of a dysfunctional VWF results in the most common inherited bleeding disorder, von Willebrand disease (VWD), and ranges in severity but predictable based on the VWD-type designation as determined by hematology reference laboratories [13]. The platelet GPIb-IX complex has been extensively characterized and is encoded by three distinct genes, the α and β subunits of GPIb and GPIX, each located on different human chromosomes [14]. Mutations in any of the three genes most commonly block intracellular assembly of the complex precluding surface expression of the entire complex or individual subunits [15]. The absence of the complex coincides with a macrothrombocytopenia with platelets observed in peripheral smears approaching the diameter of erythrocytes [16].

Direct proof the macrothrombocytopenia associated with Bernard–Soulier syndrome was the result of an absent GPIb-IX complex was established by the generation and characterization of a murine "knockout" of the GPIb α-subunit [17]. The maintenance of normal platelet size via GPIb-IX is attributed to residues within the intracytoplasmic tail of the α-subunit which directly interact with filamin-1 within the platelet cytoskeleton [18–20]. Indeed, this places GPIb-IX as an early initiator of platelet activation owing to interactions with filamin-1 [21]. Due to the macrothrombocytopenia, the mouse model of Bernard–Soulier syndrome has had limited utility for dissecting the role of GPIb-IX. Any conclusion using the model has an existing caveat that the result could be due to the absent receptor complex and/or the result of structurally abnormal "giant" platelets in reduced quantity. To circumvent this problem, a second mouse model was generated expressing an abnormal GPIb-IX lacking the adhesive domain of the α-subunit of GPIb but retaining the transmembrane and intracytoplasmic tail that still binds filamin-1 and ameliorates the macrothrombocytopenia [18]. This mouse model, designated IL-4R/Ibα^{Tg}, has become the model of choice for analyzing the pathophysiologic impact of absent GPIb-IX ligand binding function [22, 23].

Older literature exists describing an endothelial form of the platelet GPIb-IX complex [24, 25]. Later, it was proposed that the endothelial GPIb-IX complex was actually a variant complex owing to the expression of an unusual form of the β-subunit of GPIb [26]. However, this variant β-subunit was shown later to be a sequencing error and part of a variant transcript from a human septin gene residing only a few hundred nucleotides from the human β-subunit gene [27–29]. Interestingly, this placed the β-subunit gene within with the commonly mutated DiGeorge syndrome locus (22q11) with some DiGeorge syndrome patients also having a platelet Bernard–Soulier syndrome phenotype [30]. An endothelial cell version of platelet GPIb-IX is an idea that is not generally recognized or accepted today.

A role for platelet GPIb-IX in promoting tumor metastasis has been supported in mouse models of experimental metastasis and angiogenesis [31, 32]. However, an opposite conclusion was put forth by others using a different experimental approach [33]. The approaches differ with one using a genetically modified mouse, while the other used an antibody inhibitory approach in wild-type mice. While neither model is perfect, antibody inhibition of platelet GPIb-IX can lead to varying degrees of platelet activation and rapid platelet clearance [34]. It is possible that different kinetics of platelet activation and clearance may play divergent roles in tumor metastasis. Whether this explains the apparent discrepancy is not known, but clearly identifies an unmet need in our understanding of GPIb-IX in metastasis. The role of GPIb-IX as it might fit in the hallmarks of cancer will be discussed in more detail below.

Among the in vitro agonists used to stimulate platelets, type I fibrillar collagen is one of the most widely used. The best-characterized platelet membrane collagen receptors are the GPVI/FcR-γ complex and the integrin α2β1 [35–37]. The relevance of both receptors to hemostasis has been widely reported [38, 39], and both have been significantly linked to cancer pathogenesis. Again, as in the case of GPIb-IX, mouse models of GPVI deficiency have a significant reduction of metastasis using melanoma cells in models of experimental metastasis [40, 41]. However, GPVI is also known to interact with laminin and fibrin, so how much of the effect in cancer is collagen-dependent and/or other ligands is still unknown [42, 43]. A similar platelet receptor with striking similarities to GPVI is CLEC-2, and its ligand is podoplanin [44]. Here, there is also emerging data for relevance in tumor development and metastasis [45]. The same is true and perhaps even more compelling with α2β1 data. Here, the link with collagen as a matrix protein that alters the tumor microenvironment has been made along with evidence it contributes to chemoresistance [46–48].

Activation—Following adhesion, platelets undergo a level of activation that supports irreversible adhesion, inside-out signaling to activate and transform integrin receptors into high-affinity binding sites for key hemostatic ligands, such as fibrinogen. As briefly mentioned above, platelets have storage granules that can be released upon activation. Two distinct granule subtypes have been described, the α-granule and the dense granule, that release contents many of which are designed to increase the efficiency of platelet thrombus formation (49]. In general, α-granules are packed with adhesive proteins, while dense granules contain smaller molecules capable of further amplifying the platelet activation response. Among the later, ADP is particularly relevant as a common therapeutic target in cardiovascular disease.

The platelet ADP receptor, or P2Y12 receptor, becomes an activating and amplifying receptor following the release of ADP stored in platelet dense granules. Most commonly, P2Y12 antagonists are prescribed following a myocardial infarct as a therapy to reduce mortality caused by a second thrombotic event. The

inhibitors come in two varieties, thienopyridines (clopidogrel and prasugrel) and the nonthienopyridine (elinogrel, ticagrelor, and cangrelor). Large datasets are available with patients treated for their cardiovascular risk where relevance in cancer incidence can be defined. The data can be even more powerful, as some patients also receive a dual treatment of a P2Y12 inhibitor, such as clopidogrel, and a low dose or "baby" aspirin.

In one cohort, 183,912 patients with 21,974 cases of cancer were analyzed. Approximately half of the patients received aspirin only and approximately 10% received both aspirin and clopidogrel. The remainder received neither. The data established that clopidogrel and aspirin treatment were safe and led to the hypothesis that clopidogrel may reduce cancer incidence [50]. However, there are unanswered questions including whether the effects are truly platelet-dependent. The thienopyridines function as prodrugs requiring liver metabolism to generate the metabolite that irreversibly binds to the P2Y12 receptor. Is the reduction in cancer incidence the same for different types of cancers? Will similar effects be seen for the nonthienopyridines, which are not prodrugs? The ability to use the ever-expanding big data generated by the widespread use of antiplatelet cardiovascular drugs should provide expedited answers to both biological and clinically relevant questions.

While adhesion and activation platelet receptors can be ascribed to aspects of cancer development and metastasis, the tumor cell must be carefully studied as it is also able to essentially hijack normal platelet function for the benefit of survival. Data exist supporting tumor cell-induced activation of platelets [51]. For example, tumors cells release soluble platelet activating factors, such as ADP and thrombin [52, 53]. As will be described below, the platelet–tumor cell interaction driven by the tumor cell provides a distinct advantage for surviving in circulating blood. In this regard, the platelet integrin receptor, GPIIb/IIIa, becomes engaged with fibrinogen, VWF, and fibronectin creating platelet–tumor cell aggregates that are likely arrested in the microvasculature just based on size alone [51]. The IIIa, or β3 subunit, of the platelet integrin contains the RGD sequence for binding each ligand and is expressed on many cells, including tumor cells. Thus, the β3 subunit commonly found on tumor cells as part of the αvβ3 complex provides an anchoring receptor on the tumor cell side for platelet–tumor cell interactions in the circulation [54].

Aggregation—One of the most widely studied platelet receptors is the GPIIb-IIIa or αIIbβ3 integrin receptor. Interest for this receptor stems from its ability to facilitate aggregation via the prominent plasma protein, fibrinogen. As such, it brings the coagulation pathway and the role of platelets in hemostasis and thrombosis to a commonplace. Fibrinogen bridges activated platelets and support a growing platelet-rich thrombus coupled with thrombin's cleavage of fibrinogen, as part of the blood coagulation pathway, that both contribute to the generation of a stable clot. In a sense, fibrinogen becomes the mortar holding the bricks (platelets)

together in a thrombus/brick wall analogy. Thus, GPIIb/IIIa becomes an essential receptor in the hemostatic process.

Mutations in either of the integrin subunit genes encoding GPIIb/IIIa produce another human bleeding disorder referred to as Glanzmann's thrombasthenia. Not to be forgotten is the ability GPIIb/IIIa's ability to bind soluble VWF, but in the context of activated platelets the plasma concentration of fibrinogen exceeds VWF and is the more physiologically relevant adhesive ligand for GPIIb/IIIa. However, since VWF and fibrinogen are present in the platelet's secretory α-granule, full platelet activation and local ligand concentrations at the site of growing thrombus are likely to be different than those found in circulating blood. Thus, within the local milieu of a growing thrombus, the physiologic impact of VWF may be more relevant.

Interestingly, the platelet/fibrinogen axis supports metastasis in the bloodstream by limiting tumor cell lysis within micrometastases [55]. The ability of platelets to reduce tumor cell killing by natural killer (NK) cells was first demonstrated in an in vitro setting [56]. Later, with some elegant imaging and in vivo metastasis outcomes, platelets could be seen "coating" circulating tumor cells and presumably shielding the tumor cell from NK attack [57]. Given the importance of fibrinogen in these models, it might be assumed the relevant receptor supporting the interaction is GPIIb/IIIa [58].

Anti-GPIIb/IIIa therapies are available for patients undergoing percutaneous intervention [59]. The drug, abciximab, is based on a humanized antibody recognizing GPIIb/IIIa and blocking its ability to bind fibrinogen [60]. However, unlike studies with aspirin and P2Y12 antagonists, large datasets to evaluate any potential cancer effect due to abciximab are simply not available and will likely not be relevant since their current use is limited to the acute hospital setting.

Platelet Microparticles—The biological importance of platelet microparticles (PMPs) is a topic that has re-emerged since their original characterization in the 1980s [61, 62]. Originally described as platelet "dust," these smaller membrane-bound fragments of platelets have been associated with a wide range of disease processes, including being procoagulant and proinflammatory. Their relevance in cancer is likely complicated with reports of promoting angiogenesis while predisposing the cancer patient to thrombotic events. PMPs are arbitrarily defined as membrane-bound vesicles ranging from 0.5 to 1 micron in diameter. They can be identified by flow cytometry displaying platelet-specific membrane receptors [63, 64]. The platelet collagen receptor GPVI (described above) is a major contributor to PMP release in mouse models [65]. Whether the human GPVI receptor functions in a similar manner has yet to be determined.

The relevance of PMPs in angiogenesis is based on their ability to stimulate tumor cell expression of proangiogenic factors [66]. In addition, PMPs drive in vitro capillary tube formation by stimulating endothelial progenitor cells [67]. However, it is the expression of tissue factor by PMPs that is perhaps the most compelling link and clinically important link to cancer dating back to the association with venous thromboembolism by Dr. Armand Trousseau (circa 1865) and discussed below [68]. The cancer-dependent properties of PMPs along with the

ability to target platelet activation become an area requiring more detailed analysis and a topic that is likely to provide innovative insights in tumor progression and clinical management.

3.3 Hijacking of Normal Platelet Function Facilitates Steps in Hallmarks of Cancer

Cancer requires many changes, both within the tumor cell and the surrounding microenvironment, to create a permissive niche for disease progression and dissemination. In 2000, Hanahan and Weinberg defined six hallmarks of cancer: (1) self-sufficiency in growth signals, (2) insensitivity to growth-inhibitory signals, (3) resisting cell death, (4) limitless replicative potential, (5) sustained angiogenesis, and (6) metastasis [5]. In 2011, the hallmarks were updated to include not only tumor cell-intrinsic factors, but modifications within the tumor microenvironment and systemic changes that occur to fuel "a perfect storm" for tumor progression and metastatic spread. These include dysregulation of cell energetics, avoidance of immune destruction, genomic instability, and tumor-promoting inflammation [6]. Many of these hallmarks resemble the physiologic role of platelets, including within thrombosis and hemostasis, as well as the emerging role of the platelet in inflammation and immune function (Fig. 3.2).

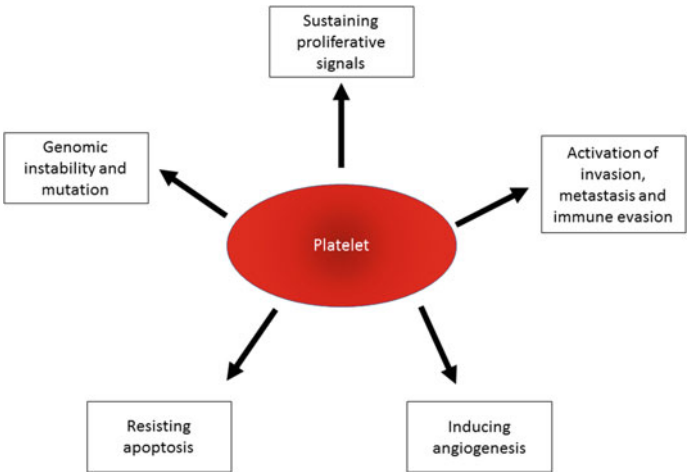

Fig. 3.2 Platelets have been demonstrated to support many of the hallmarks of cancer identified by Hanahan and Weinberg [5, 6]. Platelets can be viewed as a normal cell which contributes to the pathological development of cancer through their normal physiological functions. Antiplatelet therapies will likely represent a future direction in adjuvant cancer therapies

More than 45 years ago, it was established that thrombocytopenic mice are protected against metastasis [9]. Since then, extensive data have supported the relevance of platelets in the progression of cancer [69]. An appreciation for the relationship between blood coagulation and cancer began in the 1860s, when French physician Armand Trousseau observed an increased incidence of venous thrombosis and/or blood hypercoagulability was associated with certain cancers (Trousseau's syndrome) [68]. Trousseau later foresaw his own death from gastric cancer, when he observed a procoagulant state within his own blood. In the twentieth century, the molecular basis of Trousseau's syndrome was established with a direct demonstration of tumor cell-induced platelet aggregation [70, 71]. Subsequent work corroborated these seminal findings in a number of experimental models, each implicating a wide range of platelet receptors [72–76]. The pathophysiologic influence of circulating platelets on aspects of tumorigenesis is varied and substantial, suggesting platelet therapies typically reserved for cardiovascular disease may have profound implications in cancer, and as mentioned previously, metadata from these studies could be re-evaluated to elucidate the complicated and variable role platelets play in tumorigenesis.

Sustaining Proliferative Signals—Tumorigenesis is a multistep process which requires precise and coordinated changes in both tumor cells and the tumor microenvironment (TME). Tumor formation is often compared to a wound that does not heal, with sustained tissue proliferation and remodeling not balanced by reciprocal apoptosis. Tumor cells require constant growth signals or the ability to produce these growth signals themselves to form a primary tumor and support tumor progression. Many tumor cells acquire activating mutations in growth-sustaining signaling cascades, but these signals can also be received from the TME. Platelets have the ability to create permissive niches and release factors upon activation that can sustain these proliferative signals. Janowska-Wieczorek et al. [66] demonstrated that platelet-derived microparticles (PMPs) stimulate mitogen-activated protein kinases (MAPK) in lung carcinoma cell lines and increase cell proliferation. Mutations that lead to constitutive activation of the MAPK pathway are observed in over 30% of all malignancies and therefore not surprising that tumor cells are able to usurp activation of this pathway through mechanisms independent of genomic mutations. Further, incubating A549 lung carcinoma cells with PMPs led to increased expression of matrix metalloproteinases (MMPs) and increased invasion through Matrigel. Evasion from the primary tumor mass is a critical first step in the metastatic cascade. Platelets and the growth factors that they secrete have the ability to activate the same pathways activated through oncogenic mutations, thus driving tumorigenesis and metastasis.

Inducing Angiogenesis—Rapid proliferation and growth of tumor cells require adequate neovascularization to support blood supply for the growing tumor. It was once believed that the tumor cells were the primary suppliers of these proangiogenic factors; however, it is now clear that the tumor microenvironment and stromal cells provide significant support for creating a tumor-promoting niche, including the remodeling of surrounding vascular networks. These remodeled vascular networks not only transport in vital nutrients and provide oxygenation of the tumor, but also

remove waste, and provide access to the vascular "highway" for tumor dissemination to distant sites. Platelets have the ability to deliver many proangiogenic factors to the tumor, in addition to stimulating the tumor to express its own intrinsic angiogenic stimuli [66]. In 1998, Judah Folkman proposed that platelets provided angiogenic stimuli to the tumor and hypothesized that platelets could contribute to tumor vascular remodeling through both pro- and antiangiogenic stimuli released by platelets [77]. Indeed, loss of GPIbα in mice reduces tumor vascularization, increases tumor necrotic area, and reduces experimental metastasis of the B16 melanoma cell line (Ware, unpublished observation). Platelets are a major source of vascular endothelial growth factor (VEGF) [77, 78], platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF), all of which have been demonstrated to promote tumor growth in multiple in vitro and in vivo models [79, 80]. Platelet–tumor cell interactions can lead to the activation of platelets and stimulate the release of PMPs. Platelets and ovarian tumor cells have been shown to interact within the tumor microenvironment, the bloodstream, and in ascites fluid [81], providing angiogenic and growth-sustaining stimuli within all these microenvironments. It has been shown that VEGF, platelet factor 4, and PDGF storage in platelets are increased in colon cancer patients [82] Further, increased PMPs are found in the plasma of patients with both hematologic malignancies and solid tumors [83]. PMPs have also been shown to promote proliferation and survival of endothelial cells in both vitro and in vivo [84, 85], further supporting the creation of a proangiogenic niche to increase tumor growth and avenues for metastatic dissemination.

Activation of Invasion, Metastasis, and Immune Evasion—Metastasis is the leading cause of cancer-associated mortality and remains the greatest challenge in oncology to improving cancer prognosis and improving patient outcomes. In order for tumor cells to successful metastasize to a distant site, they must detach from the primary tumor mass, extravasate into circulation, evade the immune system and survive the shear force within the circulatory system, extravasate out of circulation into a premetastatic niche, and finally grow at that distant site. These distinct steps represent multiple opportunities for tumor cells to co-opt stromal cells and circulating cells within the vasculature, in particular platelets, to facilitate and support the metastatic cascade. Platelets have been suggested to form a protective cloak surrounding tumor cells in circulation to protect from immune surveillance and to provide protection from the shear forces present within the circulatory system [57]. These micro-emboli are likely a significant contributor to the metastatic cascade, providing protection from normal immune responses and natural killer cells [56, 57]. The "cloak" and multiple surface receptors upon the exposed platelets are also likely to play a role in these micro-emboli being able to stick to exposed endothelium, in essence docking circulating tumor cells and facilitating extravasation at distant sites. PMP releasates, as previously described, can also further enhance the ability of tumor cells to survive in the hostile environment of circulation and new environment of a distant site.

Platelets have been described to induce a mesenchymal phenotype in tumor cells through transforming growth factor β (TGFβ) signaling [86] which further facilitates a tumor cells ability to extravasate and promote metastatic seeding. In both a murine model of colon carcinoma and breast cancer cell lines, platelets were shown to prime cells for metastasis, suggesting that even brief interactions between platelets and tumor cells in vitro led to the acquisition of a tumor phenotype more permissive to metastatic seeding [86]. It was further shown that platelets were able to activate the TGFβ/Smad pathway in tumor cells, inducing an epithelial to mesenchymal transition (EMT). Direct contact between tumor cells and platelets led to increased expression of genes associated with a prometastatic phenotype, directly linking platelet–tumor cell interaction with increased propensity to metastasize. More recently, platelets have been shown to promote EMT in tumor cells through genomic transfer of miRNAs, described later.

Platelets can directly support metastasis at distant sites. Osteolytic bone metastasis in breast cancer can be stimulated by platelet-derived lysophosphatidic acid (LPA) [87]. MDA-BO2 breast cancer cells stimulate platelet aggregation and secretion of LPA, which in turn has potent paracrine effects upon the MDA-BO2 cells stimulating growth. LPA further stimulates the release of IL-6 and IL-8 from MDA-BO2, which is hypothesized to stimulate bone remodeling and osteoclast activation, supporting metastatic growth [87]. It is not clear whether platelet-derived LPA can stimulate metastasis in other tumors with tropism to bone or stimulate a permissive niche in tissue other than bone. However, these studies highlight the ability of platelets to signal through paracrine networks both with tumor cells and other stromal cells that drive the creation of permissive niches for metastatic spread.

Genomic Instability and Mutation—Platelet microparticles have been recently proposed to contain genomic material that can be transferred from platelets to recipient cells. MicroRNAs (miRNAs) from PMPs are proposed to modulate gene expression of recipient cells, thus priming stromal cells toward a protumorigenic or prometastatic phenotype. PMP transfer of miRNA-223 to endothelial cells has been shown to suppress FBXW7 and EFNA1 possibly triggering endothelial cell apoptosis [88, 89]. Transfer of miRNA-223 suppressed the expression of EPBB41L3 in lung cancer cells, resulting in increased invasiveness [90]. Additionally, miRNAs from PMPs have been shown to modulate immune surveillance miRNA-183 suppresses natural killer cell activation [91, 92] while transfer of miRNA-126-3p from platelets to primary macrophages increases their phagocytic phenotype [93]. Recently, PMP transfer of miR-939 has been shown to support EMT in ovarian cancer cells [94]. PMP secretions stimulated the proliferation and migration of SKOV3 ovarian cancer cells, and induced an EMT phenotype, hypothesized to be through the transfer of miRNA-939, which is upregulated in thrombin stimulated PMPs. The emerging role of PMPs to directly transfer genetic material and modulate expression of target genes in recipient cells needs to be confirmed in other cancer subtypes. However, it is clear that PMPs may have the ability to modulate gene signatures and induce molecular signaling that phenocopies genetic mutations.

Resisting Apoptosis—Reduction of platelet counts in nude mice injected with MDAH-2774 human ovarian cancer cells significantly reduced tumor cell apoptosis in the ascites [95]. Reduced platelet counts also reduced the number of liver nodules detected in mice with intersplenic injection of SW620 cells. Haemmerle et al. went on to demonstrate that platelets were able to stimulate $YAP1^{S127}$ and $YAP1^{S397}$ phosphorylation in cancer cells, inducing anoikis resistance and thus increased tumor cell survival in ascites. Resisting apoptosis signals not only allows the tumor to grow without restriction, but also allows disseminating tumor cells that would be susceptible to detachment-induced apoptosis to survive in hostile environments such as the ascites and circulation.

3.4 Platelet Pharmacology and Impact on Cancer, the Aspirin Studies to Date

The intracellular effects of aspirin are well established and occur via cyclooxygenase (COX) inhibition and an inability to convert arachidonic acid into prostaglandins. In the case of platelets, this inhibition blocks platelet activation, an essential step in normal hemostasis and thrombosis. Since platelets are devoid of COX-2, the platelet-dependent aspirin effect occurs exclusively via inhibition of COX-1. A major gap in our understanding of the aspirin effect is discriminating effects on platelet COX-1 from effects on COX-2, which is expressed by a wide range of other cell types including tumor cells [96, 97].

Epidemiological data do not support an anticancer effect of aspirin for all tumor types. It is not clear if this is due to insufficient data of aspirin use in all tumor types or if the antitumor effects of aspirin are tumor type-specific. Future studies will need to dissect the role of platelets and aspirin therapy in cancer prevention and tumor inhibition in multiple models of tumorigenesis. It is not yet clear whether the chemoprotective effects of aspirin on cancer prevention are tumor-specific or applicable to many tumors. Further, specificity to driver mutations has not been established, and future studies will need to incorporate the role of genetic mutation in aspirin's preventative effects [98].

As mentioned above, the antimetastatic properties of aspirin were first described in the 1970s using models of experimental metastasis [99]. However, other studies reported no such effect [100]. More recent retrospective analyses support an anticancer effect of aspirin [101–104]. Thus, the topic has once again gained interest. Understanding the risks and benefits of antiplatelet therapies in cancer patients is needed and should provide the practicing clinician with knowledge to facilitate active dialogue with patients on the best plan for treatment and care.

3.5 "Provocative" Questions and Future Studies

The plethora of historical data and modern studies clearly illustrate a dynamic orchestra that exists between platelets and cancer. Their relationship is complicated by the fact that it is not always clear whether it is causal or correlative, nor is it clear who is benefiting whom. However, it is clear that platelets and hemostasis play a critical role in cancer and that a better understanding of the dynamic mechanisms between platelets and tumors cells will allow us to leverage this knowledge for better predictive and therapeutic target identification. Collectively, the studies we have presented demonstrate how critical platelet–tumor interactions are to the initiation of disease through metastatic dissemination. Many diagnostic and prevention targets have been identified which will likely continue to revolutionize our diagnosis and treatment of cancer. We must evaluate and appreciate the critical role of the platelet in maintaining hemostasis, with the pathological role that it can play facilitating cancer, and closely evaluate the risks and benefits to the cancer patient, and tailor our interventions appropriately. Understanding the impact of thrombocytopenia or thrombocytosis on the cancer patient is clearly an area in need of an improved understanding. The National Cancer Institute and The National Heart, Lung, and Blood Institute recognized the need for improved understanding of thrombosis in cancer and convened a strategic working group to establish research priorities [105].

In 2012, the National Cancer Institute recognized the lack of understanding of the dynamic role of platelets and anticoagulants in tumorigenesis and called for applications to address with gap through the Provocative Questions Initiative. ***PQ1***: **What is the molecular mechanism by which a drug (such as aspirin) that is chronically used for other indications protects against cancer incidence and mortality?** Six years later, we have made many advances, but many gaps still exist. Future studies will need to continue to test new hypotheses and develop novel experimental systems to elucidate the relationship between platelets and tumor cells in vivo. But we must also utilize the data and resources from large population studies across disciplines, particularly the large cardiovascular studies on the protective effects of aspirin and antiplatelet therapies to reduce thrombosis. This will require collaborative efforts between basic and clinical scientists and integration of bioinformatics approaches to develop future protocols and interventions that balance the critically important physiological role of platelets with the pathologic role they can play during malignancy.

References

1. Hebda PA, Alstadt SP, Hileman WT, Eaglstein WH (1986) Support and stimulation of epidermal cell outgrowth from porcine skin explants by platelet factors. Br J Dermatol 115 (5):529–541 Epub 1986/11/01
2. Lynch SE, Nixon JC, Colvin RB, Antoniades HN (1987) Role of platelet-derived growth factor in wound healing: synergistic effects with other growth factors. Proc Natl Acad Sci USA 84(21):7696–7700 Epub 1987/11/01

3. Dvorak HF (1986) Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. N Engl J Med 315(26):1650–9. Epub 1986/12/25
4. Menter DG, Kopetz S, Hawk E, Sood AK, Loree JM, Gresele P et al (2017) Platelet first responders in wound response, cancer, and metastasis. Cancer Metastasis Rev 36(2):199–213 Epub 2017/07/22
5. Hanahan D, Weinberg RA (2000) The hallmarks of cancer. Cell 100:57–70
6. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144:646–674
7. Menter DG, Tucker SC, Kopetz S, Sood AK, Crissman JD, Honn KV (2014) Platelets and cancer: a casual or causal relationship: revisited. Cancer Metastasis Rev 33(1):231–269 Epub 2014/04/04
8. Lambert AW, Pattabiraman DR, Weinberg RA (2017) Emerging biological principles of metastasis. Cell 168(4):670–691 Epub 2017/02/12
9. Gasic GJ, Gasic TB, Stewart CC (1968) Antimetastatic effects associated with platelet reduction. Proc Natl Acad Sci USA 61:46–52
10. Gasic GJ, Gasic TB, Murphy S (1972) Anti-metastatic effect of aspirin. Lancet 2 (7783):7932–7933 Epub 1972/10/28
11. Michelson AD (ed) (2013) Platelets, 3rd edn. Academic Press, New York
12. Gresele P, Momi S, Malvestiti M, Sebastiano M (2017) Platelet-targeted pharmacologic treatments as anti-cancer therapy. Cancer Metastasis Rev 36(2):331–355 Epub 2017/07/15
13. Sharma R, Flood VH (2017) Advances in the diagnosis and treatment of Von Willebrand disease. Blood 130(22):2386–2391 Epub 2017/12/01
14. Ware J, Ruggeri ZM (2000) Platelet GPIb-IX-V complex. In: Kreis T, Vale R (eds) Guidebook to the extracellular matrix, anchor, and adhesion proteins. Oxford Unversity Press, New York, pp 288–291
15. Lopez JA, Weisman S, Sanan DA, Sih T, Chambers M, Li CQ (1994) Glycoprotein (GP) Ibβ is the critical subunit linking GP α and GP IX in the GP Ib-IX complex. J Biol Chem 269:23716–23721
16. Lopez JA, Andrews RK, Afshar-Kharghan V, Berndt MC (1998) Bernard-Soulier syndrome. Blood 91:4397–4418
17. Ware J, Russell S, Ruggeri ZM (1999) Generation and rescue of a murine model of platelet dysfunction: the Bernard-Soulier syndrome
18. Kanaji T, Russell S, Ware J (2002) Amelioration of the macrothrombocytopenia associated with the murine Bernard-Soulier syndrome. Blood 100:2102–2107
19. Kanaji T, Ware J, Okamura T, Newman PJ (2012) GPIbα regulates platelet size by controlling the subcellular localization of filamin. Blood 119:2906–2913
20. Williamson D, Pikovski I, Cranmer SL, Mangin P, Mistry N, Domagala T et al (2002) Interaction between platelet glycoprotein Ibα and filamin-1 is essential for glycoprotein Ib/IX receptor anchorage at high shear. J Biol Chem 277:2151–2159
21. Stossel TP, Condeelis J, Cooley L, Hartwig JH, Noegel A, Schleicher M et al (2001) Filamins as integrators of cell mechanics and signalling. Nat Rev Mol Cell Biol 2:138–145
22. Boulaftali Y, Hess PR, Getz TM, Cholka A, Stolla M, Mackman N et al (2013) Platelet ITAM signaling is critical for vascular integrity in inflammation. J Clin Invest 123:908–916
23. Bergmeier W, Chauhan AK, Wagner DD (2008) Glycoprotein Ibα and von Willebrand factor in primary platelet adhesion and thrombus formation: lessons from mutant mice. Thromb Haemost. 99:264–270
24. Konkle BA, Shapiro SS, Asch AS, Nachman RL (1990) Cytokine-enhanced expression of glycoprotein Ibα in human endothelium. J Biol Chem 265:19833–19838
25. Beacham DA, Tran LP, Shapiro SS (1997) Cytokine treatment of endothelial cells increases glycoprotein Ibα-dependent adhesion to von Willebrand factor. Blood 89:4071–4077
26. Konkle BA, Kelly MD, Essex DW, Meloni FJ, Shapiro SS (1992) Characterization of glycoprotein Ibβ in endothelial cells. Blood 80:1451a

27. Zieger B, Hashimoto Y, Ware J (1997) Alternative expression of platelet glycoprotein Ib(β) mRNA from an adjacent 5' gene with an imperfect polyadenylation signal sequence. J Clin Invest 99:520–525
28. Yagi M, Zieger B, Roth GJ, Ware J (1998) Structure and expression of the human septin gene HCDCREL-1. 212:229–36
29. Ware J, Martinez C, Zieger B (2008) Platelets and septins. In: Hall Russell EP, Pringle JR (eds) The Septins. Wiley, pp 269–80
30. Budarf ML, Konkle BA, Ludlow LB, Michaud D, Li M, Yamashiro DJ et al (1995) Identification of a patient with Bernard-Soulier syndrome and a deletion in the DiGeorge/velo-cardio-facial chromosomal region in 22q11.2. Hum Mol Genet 4:763–6
31. Jain S, Zuka M, Liu J, Russell S, Dent J, Guerrero J et al (2007) Platelet glycoprotein Ibα supports experimental lung metastasis. P Natl Acad Sci USA 104:9024–8
32. Kisucka J, Butterfield CE, Duda DG, Eichenberger SC, Saffaripour S, Ware J et al (2006) Platelets and platelet adhesion support angiogenesis while preventing excessive hemorrhage. Proc Natl Acad Sci USA 103:855–860
33. Erpenbeck L, Nieswandt B, Schon M, Pozgajova M, Schon MP (2010) Inhibition of platelet GPIbα and promotion of melanoma metastasis. J Invest Dermatol 130:576–586
34. Bergmeier W, Rackebrandt K, Schroder W, Zirngibl H, Nieswandt B (2000) Structural and functional characterization of the mouse von Willebrand factor receptor GPIb-IX with novel monoclonal antibodies. Blood 95:886–893
35. Clemetson KJ, Clemetson JM (2001) Platelet collagen receptors. Thromb Haemostasis 86:189–198
36. Kehrel B, Wierwille S, Clemetson KJ, Anders O, Steiner M, Knight CG et al (1998) Glycoprotein VI is a major collagen receptor for platelet activation: it recognizes the platelet-activating quaternary structure of collagen, whereas CD36, glycoprotein IIb/IIIa, and von Willebrand factor do not. Blood 91:491–499
37. Madamanchi A, Santoro SA, Zutter MM (2014) α2β1 Integrin. Adv Exp Med Biol 819:41–60 Epub 2014/07/16
38. Nieswandt B, Watson SP (2003) Platelet-collagen interaction: is GPVI the central receptor? Blood 102:449–461
39. He L, Pappan LK, Grenache DG, Li Z, Tollefsen DM, Santoro SA et al (2003) The contributions of the α2 and β1 integrin to vascular thrombosis in vivo. Blood 102:3652–3657
40. Farndale RW (2009) Platelet glycoprotein VI as a mediator of metastasis. J Thromb Haemost 7:1711–1712
41. Jain S, Russell S, Ware J (2009) Platelet glycoprotein VI facilitates experimental lung metastasis in syngenic mouse models. J Thromb Haemost 7:1713–1717
42. Inoue O, Suzuki-Inoue K, McCarty OJ, Moroi M, Ruggeri ZM, Kunicki TJ et al (2006) Laminin stimulates spreading of platelets through integrin α6β1-dependent activation of GPVI. Blood 107:1405–1412
43. Alshehri OM, Hughes CE, Montague S, Watson SK, Frampton J, Bender M et al (2015) Fibrin activates GPVI in human and mouse platelets. Blood 126(13):1601–1608 Epub 2015/08/19
44. Watson SP, Herbert JM, Pollitt AY (2010) GPVI and CLEC-2 in hemostasis and vascular integrity. J Thromb Haemost 8:1456–1467
45. Lowe KL, Navarro-Nunez L, Watson SP (2012) Platelet CLEC-2 and podoplanin in cancer metastasis. Thromb Res 129(Suppl):30–37
46. Ramirez NE, Zhang Z, Madamanchi A, Boyd KL, O'Rear LD, Nashabi A et al (2011) The α(2)β(1) integrin is a metastasis suppressor in mouse models and human cancer. J Clin Invest 121(1):226–237 Epub 2010/12/08
47. Zutter MM (2007) Integrin-mediated adhesion: tipping the balance between chemosensitivity and chemoresistance. Adv Exp Med Biol 608:87–100 Epub 2007/11/13

48. Naci D, Vuori K, Aoudjit F (2015) α2β1 integrin in cancer development and chemoresistance. Semin Cancer Biol 35:145–153 Epub 2015/08/25
49. Yadav S, Storrie B (2017) The cellular basis of platelet secretion: emerging structure/function relationships. Platelets 28(2):108–118 Epub 2016/12/25
50. Leader A, Zelikson-Saporta R, Pereg D, Spectre G, Rozovski U, Raanani P et al (2017) The effect of combined aspirin and clopidogrel treatment on cancer incidence. Am J Med 130 (7):826–832 Epub 2017/02/19
51. Kitagawa H, Yamamoto N, Yamamoto K, Tanoue K, Kosaki G, Yamazaki H (1989) Involvement of platelet membrane glycoprotein Ib and glycoprotein IIb/IIIa complex in thrombin-dependent and -independent platelet aggregations induced by tumor cells. Cancer Res 49(3):537–541 Epub 1989/02/01
52. Zucchella M, Dezza L, Pacchiarini L, Meloni F, Tacconi F, Bonomi E et al (1989) Human tumor cells cultured in vitro activate platelet function by producing ADP or thrombin. Haematologica 74(6):541–545 Epub 1989/11/01
53. Boukerche H, Berthier-Vergnes O, Penin F, Tabone E, Lizard G, Bailly M et al (1994) Human melanoma cell lines differ in their capacity to release ADP and aggregate platelets. Br J Haematol 87(4):763–772 Epub 1994/08/01
54. Felding-Habermann B, Habermann R, Saldivar E, Ruggeri ZM (1996) Role of β3 integrins in melanoma cell adhesion to activated platelets under flow. J Biol Chem 271:5892–5900
55. Degen JL, Palumbo JS (2012) Hemostatic factors, innate immunity and malignancy. Thromb Res 129(Suppl 1):1–5 Epub 2012/06/15
56. Nieswandt B, Hafner M, Echtenacher B, Mannel DN (1999) Lysis of tumor cells by natural killer cells in mice is impeded by platelets. Cancer Res 59:1295–1300
57. Palumbo JS, Talmage KE, Massari JV, La Jeunesse CM, Flick MJ, Kombrinck KW et al (2005) Platelets and fibrin(ogen) increase metastatic potential by impeding natural killer cell-mediated elimination of tumor cells. Blood 105:178–185
58. Palumbo JS, Kombrinck KW, Drew AF, Grimes TS, Kiser JH, Degen JL et al (2000) Fibrinogen is an important determinant of the metastatic potential of circulating tumor cells. Blood 96:3302–3309
59. Goklaney AK, Murphy JD, Hillegass WB Jr (1998) Abciximab therapy in percutaneous intervention: economic issues in the United States. Am Heart J 135(4):90–97 Epub 1998/04/16
60. Coller BS (2001) Anti-GPIIb/IIIa drugs: current strategies and future directions. Thromb Haemost 86(1):427–443 Epub 2001/08/07
61. Wiedmer T, Esmon CT, Sims PJ (1986) Complement proteins C5b-9 stimulate procoagulant activity through platelet prothrombinase. Blood 68(4):875–880 Epub 1986/10/01
62. Sandberg H, Bode AP, Dombrose FA, Hoechli M, Lentz BR (1985) Expression of coagulant activity in human platelets: release of membranous vesicles providing platelet factor 1 and platelet factor 3. Thromb Res 39(1):63–79 Epub 1985/07/01
63. Sims PJ, Faioni EM, Wiedmer T, Shattil SJ (1988) Complement proteins C5b-9 cause release of membrane vesicles from the platelet surface that are enriched in the membrane receptor for coagulation factor Va and express prothrombinase activity. J Biol Chem 263 (34):18205–18212 Epub 1988/12/05
64. Abrams CS, Ellison N, Budzynski AZ, Shattil SJ (1990) Direct detection of activated platelets and platelet-derived microparticles in humans. Blood 75(1):128–138 Epub 1990/01/01
65. Boilard E, Nigrovic PA, Larabee K, Watts GF, Coblyn JS, Weinblatt ME et al (2010) Platelets amplify inflammation in arthritis via collagen-dependent microparticle production. Science 327:580–583
66. Janowska-Wieczorek A, Wysoczynski M, Kijowski J, Marquez-Curtis L, Machalinski B, Ratajczak J et al (2005) Microvesicles derived from activated platelets induce metastasis and angiogenesis in lung cancer. IntJCancer. 113:752–760

67. Prokopi M, Pula G, Mayr U, Devue C, Gallagher J, Xiao Q et al (2009) Proteomic analysis reveals presence of platelet microparticles in endothelial progenitor cell cultures. Blood 114 (3):723–732 Epub 2009/04/17
68. Varki A (2007) Trousseau's syndrome: multiple definitions and multiple mechanisms. Blood 110:1723–1729
69. Gay LJ, Felding-Habermann B (2011) Contribution of platelets to tumour metastasis. Nat Rev Cancer 11:123–134
70. Gasic GJ, Gasic TB, Galanti N, Johnson T, Murphy S (1973) Platelet-tumor-cell interactions in mice. The role of platelets in the spread of malignant disease. Int J Cancer 11:704–18
71. Karpatkin S, Pearlstein E, Ambrogis C, Coller BS (1988) Role of adhesive proteins in platelet tumor interaction in vitro and metastasis formation in vivo. J Clin Invest 81:1012–1019
72. Bakewell SJ, Nestor P, Prasad S, Tomasson MH, Dowland N, Mehrotra M et al (2003) Platelet and osteoclast β3 integrins are critical for bone metastasis. Proc Natl Acad Sci USA 100:14205–14210
73. Jain S, Harris J, Ware J (2010) Platelets: Linking hemostasis and cancer. Arterioscler Thromb Vasc Biol 30:2362–2367
74. Kim YJ, Borsig L, Varki NM, Varki A (1998) P-selectin deficiency attenuates tumor growth and metastasis. Proc Natl Acad Sci USA 95:9325–9330
75. Labelle M, Hynes RO (2012) The initial hours of metastasis: the importance of cooperative host-tumor cell interactions during hematogenous dissemination. Cancer Discov 2:1091–1099
76. Palumbo JS, Degen JL (2007) Mechanisms linking tumor cell-associated procoagulant function to tumor metastasis. Thromb Res 120(Suppl):22–28
77. Pinedo HM, Verheul HM, D'Amato RJ, Folkman J (1998) Involvement of platelets in tumour angiogenesis? Lancet 352:1775–1777
78. Verheul HM, Hoekman K, Luykx-de Bakker S, Eekman CA, Folman CC, Broxterman HJ et al (1997) Platelet: transporter of vascular endothelial growth factor. Clin Cancer Res 3:2187–2190
79. Cross MJ, Claesson-Welsh L (2001) FGF and VEGF function in angiogenesis: signalling pathways, biological responses and therapeutic inhibition. Trends Pharmacol Sci 22:201–207
80. Ferrara N, Gerber HP, LeCouter J (2003) The biology of VEGF and its receptors. Nat Med 9:669–676
81. Stone RL, Nick AM, McNeish IA, Balkwill F, Han HD, Bottsford-Miller J et al (2012) Paraneoplastic thrombocytosis in ovarian cancer. N Engl J Med 366:610–618
82. Peterson JE, Zurakowski D, Italiano JE Jr, Michel LV, Connors S, Oenick M et al (2012) VEGF, PF4 and PDGF are elevated in platelets of colorectal cancer patients. Angiogenesis 15:265–273
83. Mezouar S, Mege D, Darbousset R, Farge D, Debourdeau P, Dignat-George F et al (2014) Involvement of platelet-derived microparticles in tumor progression and thrombosis. Semin Oncol 41:346–358
84. Kim HK, Song KS, Chung JH, Lee KR, Lee SN (2004) Platelet microparticles induce angiogenesis in vitro. Br J Haematol 124:376–384
85. Varon D, Shai E (2009) Role of platelet-derived microparticles in angiogenesis and tumor progression. Discov Med 8:237–241
86. Labelle M, Begum S, Hynes RO (2011) Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis. Cancer Cell 20:576–590
87. Boucharaba A, Serre CM, Gres S, Saulnier-Blache JS, Bordet JC, Guglielmi J et al (2004) Platelet-derived lysophosphatidic acid supports the progression of osteolytic bone metastases in breast cancer. J Clin Invest 114:1714–2175

88. Laffont B, Corduan A, Ple H, Duchez AC, Cloutier N, Boilard E, et al (2013) Activated platelets can deliver mRNA regulatory Ago2 microRNA complexes to endothelial cells via microparticles. Blood 122(2):253–61
89. Pan Y, Liang HW, Liu H, Li DH, Chen X, Li LM et al (2014) Platelet-Secreted MicroRNA-223 promotes endothelial cell apoptosis induced by advanced glycation end products via targeting the insulin-like growth factor 1 receptor. J Immunol 192(1):437–446
90. Liang HW, Yan X, Pan Y, Wang YS, Wang N, Li LM, et al (2015) MicroRNA-223 delivered by platelet-derived microvesicles promotes lung cancer cell invasion via targeting tumor suppressor EPB41L3. Mol Cancer 14
91. Donatelli SS, Zhou JM, Gilvary DL, Eksioglu EA, Chen XH, Cress WD et al (2014) TGF-β-inducible microRNA-183 silences tumor-associated natural killer cells. P Natl Acad Sci USA 111(11):4203–4208
92. Sadallah S, Schmied L, Eken C, Charoudeh HN, Amicarella F, Schifferli JA (2016) Platelet-derived ectosomes reduce NK cell function. J Immunol 197(5):1663–1671
93. Laffont B, Corduan A, Rousseau M, Duchez AC, Lee CHC, Boilard E et al (2016) Platelet microparticles reprogram macrophage gene expression and function. Thromb Haemostasis 115(2):311–323
94. Tang ML, Jiang L, Lin YY, Wu XL, Wang K, He QZ et al (2017) Platelet microparticle-mediated transfer of miR-939 to epithelial ovarian cancer cells promotes epithelial to mesenchymal transition. Oncotarget 8(57):97464–97475
95. Haemmerle M, Taylor ML, Gutschner T, Pradeep S, Cho MS, Sheng JT, et al (2017) Platelets reduce anoikis and promote metastasis by activating YAP1 signaling. Nat Commun 8
96. Bruno A, Dovizio M, Tacconelli S, Patrignani P (2012) Mechanisms of the antitumoural effects of aspirin in the gastrointestinal tract. Best Pract Res Clin Gastroenterol 26:e1–e13
97. Kaiser J (2012) Will an aspirin a day keep cancer away? Science 337:1471–1473
98. Maity G, De A, Das A, Banerjee S, Sarkar S, Banerjee SK (2015) Aspirin blocks growth of breast tumor cells and tumor-initiating cells and induces reprogramming factors of mesenchymal to epithelial transition. Lab Invest 95:702–717
99. Kolenich JJ, Mansour EG, Flynn A (1972) Haematological effects of aspirin. Lancet 2:714
100. Jr WS, Hilgard P (1972) Aspirin and tumour metastasis. Lancet 2:1416–1417
101. Bowers LW, Maximo IX, Brenner AJ, Beeram M, Hursting SD, Price RS et al (2014) NSAID use reduces breast cancer recurrence in overweight and obese women: role of prostaglandin-aromatase interactions. Cancer Res 74:4446–4457
102. Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW (2011) Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet 377:31–41
103. Rothwell PM, Price JF, Fowkes FG, Zanchetti A, Roncaglioni MC, Tognoni G et al (2012) Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet 379:1602–1612
104. Rothwell PM, Wilson M, Price JF, Belch JF, Meade TW, Mehta Z (2012) Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. Lancet 379:1591–1601
105. Key NS, Khorana AA, Mackman N, McCarty OJT, White GC, Francis CW et al (2016) Thrombosis in cancer: research priorities identified by a National Cancer Institute/National Heart, Lung, and Blood Institute Strategic Working Group. Can Res 76(13):3671–3675

4 Risk of Thrombosis in Cancer: Clinical Factors and Role of Primary Prophylaxis

Joanna Roopkumar and Alok A. Khorana

Contents

J. Roopkumar · A. A. Khorana (✉)
Taussig Cancer Institute Cleveland Clinic, 10201 Carnegie Ave, CA60, Cleveland, OH 44195, USA
e-mail: khorana@ccf.org

G. Soff (ed.), *Thrombosis and Hemostasis in Cancer*, Cancer Treatment and Research 179, https://doi.org/10.1007/978-3-030-20315-3_4

4.1 Introduction

Thromboembolism in cancer is a problem of major public health concern worldwide. Venous thromboembolism (VTE) is a major cause of morbidity and mortality in patients with cancer [1]. Cancer is responsible for nearly one-fifth of all cases of incident VTE. Across all patients with cancer, the risk for VTE is elevated sevenfold; in certain subgroups such as specific primary sites of cancer, the risk for VTE may be increased up to 28-fold [2]. Although it is commonly stated that one in five cancer patients will develop VTE during the course of the disease, the converse is less commonly acknowledged: Four in five cancer patients will *not* develop VTE. In other words, there is substantial variation in risk between individual cancer patients and subgroups as well as settings of cancer patients. This concept has led researchers over the past decade to develop formal risk assessment tools and approaches to identifying cancer patients especially at risk for VTE [3].

Venous thromboembolism is a potentially preventable illness with several agents and classes of drugs that have been demonstrated to safely do so [4]. Primary thromboprophylaxis is an important development in the supportive care of cancer, with established criteria for certain settings such as surgery or hospitalization for medical illness. However, the vast majority of cancer patients are seen, and develop VTE, in the outpatient setting where thromboprophylaxis is not currently routine. This chapter will focus on identifying cancer patients at high risk for VTE and offer an overview of utilizing risk stratification as a way to safely and effectively select patients for thromboprophylaxis.

4.2 Clinical Risk Factors

Many risk factors have known to be linked with cancer-associated thrombosis, and they can be broadly classified into cancer-specific, patient-specific, treatment-specific, and biomarker-specific factors [2].

4.2.1 Cancer-Specific Factors

4.2.1.1 Primary Site of Cancer

Many studies have found the primary site of cancer to have a significant effect on VTE rates on cancer patients. In a study from the California Cancer Registry, the development of VTE was particularly high for patients with cancer of the pancreas, stomach, kidney, bladder, uterus, and lung [5]. The variation in rates was striking: VTE occurred in 20 and 10.7% of patients with advanced pancreas and stomach cancers, respectively, but only 0.9 and 2.8% of patients with advanced prostate and breast cancers, respectively [5]. In 2005, a large population-based, case-control

study of 3220 patients in Netherlands reported that hematological malignancies had the highest risk of venous thrombosis, adjusted for age and sex (adjusted OR, 28.0; 95% CI, 4.0-199.7), followed by lung cancer and gastrointestinal cancer [6]. In another recent population-based study in Denmark, the incidence rates of VTE among patients with subtypes of hematological cancer were studied and increased in all types of hematological cancer (including chronic lymphocytic leukemia) compared with reference subjects except indolent lymphomas [2]. Even within the same primary site of cancer, rates of VTE can vary by histological sub-type. In a study of the lung cancer cohort from the California Cancer Registry discussed above, among patients with non-small-cell lung cancer, rates of VTE were high in adenocarcinoma (HR = 1.9) compared to those with squamous cell carcinoma (95% CI = 1.7–2.1) [7].

4.2.1.2 Stage of Cancer

The stage of cancer has been associated with the rate of VTE in cancer. Among surgical oncology patients, advanced stage was found to be associated with increased risk of VTE (OR = 2.7; 95% CI, 1.4–5.2), although it is not clear if this is related to tumor burden or the association of advanced stage with poor performance status and greater use of therapeutic interventions, particularly prolonged systemic therapy [8]. Indeed, in ambulatory cancer patients with good performance status receiving chemotherapy, stage was not identified to be a predictor of VTE [9]. Similarly, in another study of ovarian cancer patients, there was no association between stage of cancer and VTE [10].

4.2.1.3 Time Period After Diagnosis

The risk of VTE has been identified to be highest in the period following the initial diagnosis of cancer. In a large population-based study, the risk of VTE was highest in the first few months after the diagnosis of malignancy (adjusted OR, 53.5; 95% CI, 8.6–334.3) [6]. Only 2 years after initial diagnosis did the relative risk of developing VTE decrease and yet remained higher than in individuals without cancer. The etiology of this increased risk is unclear and may be related to either the biology of cancer, or to the increased number of therapeutic interventions including biopsies, surgical resection, placement of central venous catheters, and initiation of systemic therapy all of which are more likely in this early phase of diagnosis and treatment [6].

4.2.2 Patient-Specific Factors

4.2.2.1 Patient Demographics

Patient-specific factors such as age, race, and sex may also contribute to risk of VTE in cancer. In a study of 2373 surgical oncology patients, VTE occurred more frequently in patients older than 60 years of age (OR of VTE was 2.6 (95% CI,

1.2–5.7) [8]. However, among ambulatory cancer patients, age was not significantly associated with VTE when the study population had a good performance status [9]. Overall there was no association found between sex and VTE rates; however, one study in hospitalized oncology patients found an increased risk of VTE in women [11]. Studies have demonstrated some association between race and rates of VTE, with African Americans found to have increased risk compared to Asians/Pacific Islanders [12]. However, this has not been demonstrated in other studies, for instance in an analysis of the placebo arm of a global thromboprophylaxis trial [12].

4.2.2.2 Performance Status

Immobility by itself is a known risk factor for VTE irrespective of the presence of cancer. The rates of VTE were found to be significantly higher for surgical oncology patients who were on a bed rest for a period longer than 3 days [8]. In the patient group with the first episode of VTE (n = 223), performance status (a surrogate for mobility) showed a nonsignificant trend of higher rates of VTE in patients with poor performance status [1].

4.2.2.3 Comorbid Conditions

The presence of medical comorbidities greatly impacts the risk of VTE in cancer patients. Some of the comorbidities that are strongly associated include infection (OR = 1.8), arterial thromboembolism (OR = 1.5), renal disease (OR = 1.5), pulmonary disease (OR = 1.4), and anemia (OR = 2.4) [2]. Also, past history of thrombosis and obesity are well-known risk factors for VTE [2].

4.2.3 Treatment-Related Factors

The different treatment-related factors that influence risk of VTE in cancer include systemic therapy, hospitalization, surgery, central venous catheters (CVCs), supportive therapy, and radiation. Surgery is a known risk factor of VTE in all patients. In a recent study of cancer surgical patients, risk factors for postoperative VTE included age more than 60 years (OR-2.6; 95%CI, 1.2–5.7), previous VTE (OR-6.0; 95% CI, 2.1–16.8), advanced cancer (OR-2.7; 95% CI, 1.4–5.2), anesthesia lasting more than 2 h (OR-4.5; 95% CI, 1.1–19), and bed rest longer than 3 days (OR-4.4; 95% CI, 2.5–7.8) [7].

Chemotherapy is associated with a two-to-sixfold increase in VTE risk compared to the general population. Platinum-based drugs are significantly associated with VTE with higher rates for cisplatin compared to oxaliplatin [13]. CVCs are associated with VTE, and the main risk factors include more than one insertion attempt, previous CVC insertion, left-sided placement, catheter tip position in the superior vena cava compared with right atrium and arm ports compared with chest ports. Infusion of antineoplastic agent through the port has also found to increase the rate of catheter-associated DVT [2].

Bevacizumab, an antiangiogenic agent which acts against vascular endothelial growth factor (VEGF), has shown to be effective against several cancers [14]. Several clinical trials have identified bevacizumab to be associated with arterial thromboembolic events. Other VEGF tyrosine kinase inhibitors like sunitinib and sorafenib have been shown to increase arterial thrombotic complications (RR, 3.0; 95% CI, 1.25–7.37; $P = 0.015$) [15].

4.3 Biomarkers

The various biomarkers that have been known to be associated with VTE include platelet and leukocyte counts, tissue factor (TF), D-dimer, C-reactive protein, and soluble-P-selectin. For patients initiating a new chemotherapy regimen, elevated platelet and leukocyte counts have been shown to be associated with increased VTE risk [16]. For patients with pancreatic cancer, high TF expression in tumor tissue has shown to be associated with increased VTE as well. However, it is unclear whether TF is a biomarker for VTE in non-pancreatic cancer patients. Elevated D-dimer levels are shown to be associated with recurrent VTE in cancer patients (HR, 1.8; 95% CI, 1.0–3.2; $P = 0.048$). Elevated C-reactive protein of more than 400 mg/dl has been associated with the development of VTE in a prospective single-institution observational study of 507 patients. In newly diagnosed or recurrent cancer patients, elevated P-selectin levels of more than 53.1 ng/mL were predictive of VTE [17].

4.4 Risk Assessment Scores for Cancer-Associated VTE

In 2008, a validated risk assessment tool now known as the "Khorana score" was developed to stratify VTE risk in cancer patients (Table 1). The five patient characteristics used in this score are all universally available clinical parameters:

Table 1 Predicting risk of treatment-associated venous thromboembolism in cancer (Khorana score) [16]

Patient characteristic	Risk score
Site of cancer Very high risk (stomach, pancreas) High risk (lung, lymphoma, gynecologic, bladder, testicular)	2 1
Prechemotherapy platelet count $\geq$ 350,000/μL	1
Hemoglobin level < 10 g/dL or use of red cell growth factors	1
Prechemotherapy leukocyte count > 11,000/μL	1
Body mass index $\geq$ 35 kg/m2	1

High risk defined as score of greater than or equal to 3

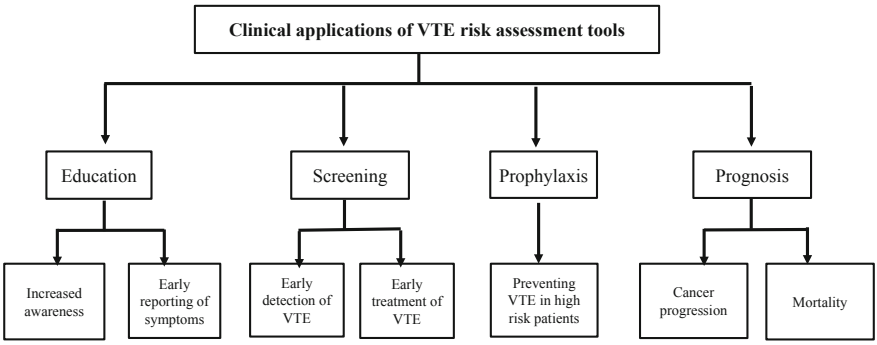

Fig. 1 Various applications of risk assessment for VTE in cancer [18]

(1) primary site of cancer, (2) pre-chemotherapy platelet count, (2) hemoglobin level, (3) pre-chemotherapy leukocyte count, and (4) body mass index. The risk score was categorized into three categories: low (score 0), intermediate (score 1–2), and high (score $\geq$ 3). This model had a negative predictive value of 98.5%, positive predictive value of 7.1%, sensitivity of 40%, and specificity of 88%. This tool has been studied widely for the screening, identification, selection, and exclusion of patients for thromboprophylaxis and early detection of VTE [16]. The various clinical applications of this risk model are described in Fig. 1. Recently, multiple new papers have attempted to modify or create new prediction tools, most of which are still unvalidated but point to ways that risk assessment can be further streamlined (Table 2).

4.5 Venous Thromboembolism Prophylaxis in Patients with Cancer

The different expert panels such as American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), the International Society of Thrombosis and Hemostasis (ISTH), the European Society of Medical Oncology (ESMO), the International Initiative on Thrombosis and Cancer (ITAC) have all issued guidelines on the prophylaxis of cancer-associated thrombosis in major groups of cancer patients including surgical and postsurgical patients, hospitalized medical patients, outpatients and patients with indwelling catheters, with large areas of consensus between the various panels. Current guideline for prophylaxis of VTE in cancer patients in various settings is shown in Table 3.

Table 2 Select risk scores for cancer-associated VTE and their characteristics [19]

Risk score	Innovation/modification	Validated?	Improves prediction?	Predicts benefit from thromboprophylaxis?	Identifies early VTE?	Predicts VTE once chemotherapy already initiated?	Predicts inpatient VTE?
Khorana	(Original)	Yes	(reference)	Yes	Yes	Unknown	Yes
Vienna [20]	Adds D-dimer, sP-selectin	No	Yes[a] (improved PPV)	Unknown	Unknown	Unknown	Unknown
Protecht [21]	Removes body mass index, adds chemotherapy	No	Unclear	Yes	Unknown	Unknown	Unknown
ONKOTEV [22]	Adds variables: metastatic disease, prior VTE, compression	No	Yes[a] (improved AUC)	Unknown	Unknown	Unknown	Unknown
COMPASS-CAT [23]	Breast, colorectal, lung, ovarian only	Lung only	Yes[a] (improved AUC)	Unknown	Unknown	Unknown	Unknown
Tic-ONCO [24]	Adds genetic risk factors	No	Yes[a] (improved AUC, PPV)	Unknown	Unknown	Unknown	Unknown
Pabinger et al. [25]	Adds D-dimer, removes all other variables except site	Yes	Yes[a] (improved PPV)	Unknown	Unknown	Yes	Unknown

[a]Pending further validation
AUC area under curve
PPV positive predictive value

Table 3 Current guidelines recommendations for prophylaxis of VTE in cancer patients in various settings

	Hospitalized medical cancer patients	Cancer outpatients	Surgical cancer patients
ASCO [26]	LMWH for duration of hospitalization, for patients with acute medical illness	Not routinely recommended except in high-risk patients on case-by-case basis, e.g., Khorana score $\geq$ 3 or pancreas cancer	Pre-operative LMWH and postoperative LMWH for 7–10 days in low risk patients and up to 4 weeks in high-risk patients
NCCN [27[	UFH and pneumatic venous compression device	Not routinely recommended except in high-risk patients	Postoperative LMWH up to 4 weeks
ISTH [28]	LMWH for the course of the hospital admission and not recommended for patients admitted for minor illness	Not routinely recommended except in high-risk patients	Postoperative LMWH

4.5.1 Surgical Patients

Clinical trials have shown the efficacy of low-dose unfractioned heparin (UFH) in preventing DVT and PE in nearly all patients undergoing major surgery without significantly increasing bleeding complications. Low-molecular-weight heparin (LMWH) has a more predictable anticoagulant response than UFH, a longer plasma half-life, better bioavailability when administered subcutaneously, and the convenience of once-daily dosing. A meta-analysis incorporating 16 randomized trials with 12,890 patients with cancer showed no difference in either safety or efficacy comparing prophylactic LMWH to UFH in postoperative setting [2]. Current guidelines recommend extended prophylaxis after major abdominal pelvic cancer surgery. A full discussion of the approach to surgical prophylaxis is found elsewhere in this text.

4.5.2 Hospitalized Medical Cancer Patients

No cancer-specific studies of thromboprophylaxis in hospitalized cancer patients have been conducted, so recommendations are derived largely from studies involving general medical patients. Three large randomized, double-blind, placebo-controlled trials in acutely ill medical patients demonstrated reduced rates of VTE with the use of prophylactic LMWH or fondaparinux [29]. These studies reported an absolute risk reduction of 2–10% in the incidence of symptomatic and screen-detected VTE over a 3-month follow-up period. However, cancer patients represented a minority of the patients in these studies. This remains a major knowledge gap in the area. Current ASCO guidelines recommend LMWH for

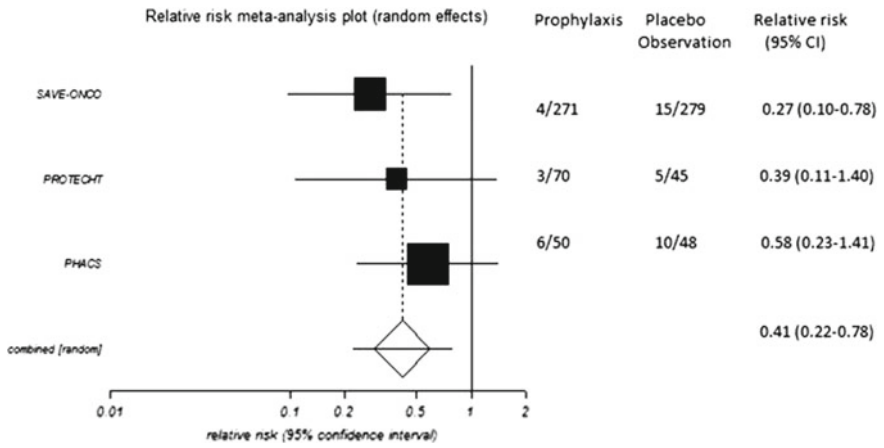

Fig. 2 Forest plot and pooled estimates of the relative risk of VTE in cancer patients with Khorana score $\geq$ 3 assigned to thromboprophylaxis or placebo in subgroup analyses of prior randomized trials; relative risk for VTE with thromboprophylaxis was 0.41 (95% CI: 0.22–0.78; p = 0.006) in a random effects model (From Khorana et al. [32])

hospitalized medical patients with an acute medical illness but not for cancer patients admitted for routine procedures [26].

4.5.3 Cancer Outpatients

Major studies focusing on outpatient thromboprophylaxis for solid tumor or myeloma patients receiving systemic therapy have been reported. The prophylaxis of thromboembolism during chemotherapy trial (PROTECHT) evaluated the efficacy of daily administration of nadroparin, a LMWH, in patients with cancer at "high-risk" sites, including those with locally advanced or metastatic lung, gastrointestinal (GI), pancreatic, breast, ovarian, and head/neck cancers who were actively receiving chemotherapy. Event rates were low: 2% of the treatment group and 3.9% of the placebo group experienced a thromboembolic event (one-sided 95% CI, 0.303%; P = 0.02), with a nonsignificant increase in major bleeding. Similar low event rates were reported with the SAVE-ONCO trial which utilized an ultra-low-molecular-weight heparin, semuloparin [30]. Other randomized controlled trials focused on specific cancer types, particularly pancreas, and showed a substantial absolute and relative risk reduction in VTE [31].

In a recent study, cancer patients with Khorana score $\geq$ 3 starting a new systemic regimen were screened for VTE and if negative randomized to dalteparin 5000 units daily or observation for 12 weeks. Subjects were screened with lower extremity ultrasound every 4 weeks on study and with chest CT at 12 weeks. Thromboprophylaxis was associated with a non-significantly reduced risk of VTE and significantly increased risk of clinically relevant bleeding in this study [32]. In a

pooled analysis of various trials that have provided data on subgroups of patients with risk score of 3 or higher, the pooled relative risk for VTE with thromboprophylaxis was 0.41 (95% CI: 0.22–0.78; $p = 0.006$) in a random effects model (Fig. 2) [32].

The potential role of direct oral anticoagulants (DOACs) in prevention of cancer-associated VTE is the subject of two large randomized studies that recently completed analyses [33, 34]. The only published trial prior to this was a pilot study of 125 patients, in which 3 of 29 (10.3%) of placebo-treated patients developed VTE compared to none of 93 apixaban treated patients, in three different dosing cohorts. No major bleeding incidents were reported with either a 5 or 10 mg dose of apixaban, but two (6.3%) of 32 patients had a major bleed in the 20 mg group [35]. Currently, routine thromboprophylaxis is not recommended for cancer patients in the outpatient setting except a selective high-risk patient group [26].

The two most recent landmark studies in the outpatient setting are CASSINI and AVERT [33, 34]. CASSINI was a double-blinded, randomized, placebo-controlled, parallel-group, multicenter trial in adult ambulatory patients, receiving new systemic therapy for their cancer diagnoses who are at increased risk for venous thromboembolism (VTE) with a Khorana score of 2 or higher. All patients underwent baseline screening ultrasonography of lower extremities prior to randomization, and interestingly, 4.5% already had a preexisting but asymptomatic DVT and were not randomized. Patients without DVT were randomized 1:1 to either rivaroxaban 10 mg once daily or placebo for up to 180 days. Primary efficacy endpoint included DVT, PE, and VTE-related deaths, including screen-detected DVT (lower extremity screening ultrasonography conducted every 8 weeks on study). The primary safety endpoint was major bleeding. Overall, 841 patients were randomized to rivaroxaban ($n = 420$) or placebo ($n = 421$). Rivaroxaban significantly reduced VTE and VTE-related deaths during the on-treatment period [11 of 420 patients (2.62%) in rivaroxaban and 27 of 421 (6.41%) in placebo group (HR 0.40, 95% CI 0.20–0.80, $p = 0.007$)] (number needed to treat, NNT = 26) but not during the full study period [25 of 420 patients (5.95%) in rivaroxaban and 37 of 421 (8.79%) in placebo group (HR 0.66, 95% CI 0.40–1.09, $p = 0.101$) (NNT = 35). The primary safety endpoint of major bleeding occurred in 8 of 405 (1.98%) in the rivaroxaban group and in 4 of 404 (0.99%) patients in the placebo group (HR, 1.96; 95% CI, 0.59–6.49; $p = 0.265$) (number needed to harm, NNH = 101). Clinically relevant non-major bleeding occurred in 2.72 and 1.98% of rivaroxaban and placebo groups, respectively (HR, 1.34; 95% CI, 0.54–3.32; $p = 0.53$) (NNH = 135). A pre-specified composite of the primary endpoint with all-cause mortality showed a significant reduction with rivaroxaban [23.1% in rivaroxaban group and 29.5% in placebo group (HR 0.75, 95% CI 0.57–0.97, $p = 0.03$)] [33].

The second study, AVERT, studied the efficacy of apixaban to prevent VTE in cancer patients in the ambulatory setting [34]. Study eligibility was similar to CASSINI with a focus on ambulatory cancer patients with a Khorana score of 2 or higher and with primary efficacy outcome of VTE over a period of 180 days and primary safety outcome of major bleeding. However, AVERT did not involve baseline or on-study ultrasonography screening. Overall, 574 patients were

randomized to receive either apixaban (n = 288) 2.5 mg twice daily or placebo (n = 275). The primary efficacy outcome of VTE occurred in significantly fewer patients (4.2%) in the apixaban group compared to 10.2% in the placebo group [HR, 0.41; 95% CI, 0.26–0.65; $p < 0.001$] (NNT = 17). Major bleeding during the treatment period occurred in 6 of 288 patients (2.1%) in the apixaban group and 3 of 275 patients (1.1%) in the placebo group (HR, 1.89; 95% CI, 0.39–9.24) (NNH = 100) [34].

Together, these findings demonstrate clear benefit to cancer patients with a primary prevention approach with small risk of harm. Given the favorable NNT/NNH ratios in both CASSINI and AVERT, individual patients would be likely to benefit from outpatient thromboprophylaxis; the absolute risk reductions observed here are among the highest seen in any medical thromboprophylaxis study. The potential reduction in mortality observed in CASSINI, but not in AVERT suggests that baseline screening for preexisting DVT may further add to net benefit of prophylaxis by identifying patients who need therapeutic doses of anticoagulation and focusing on a true thrombosis-free population for benefit of thromboprophylaxis. Together, these findings should inform future guidelines on outpatient thromboprophylaxis and change practice to reduce the public health burden of VTE and potentially arterial events in cancer patients.

4.5.4 Cancer Patients with Indwelling Catheters

Strategies for the prevention of venous catheter-associated thrombosis in patients with cancer have also been studied. These approaches have evaluated the use of a vitamin K antagonist at a fixed low dose (1 mg/day), a vitamin K antagonist with dosage adjusted to maintain a target international normalized ratio (INR), UFH, and LMWH. A meta-analysis by Akl e al. summarized the findings of nine of these studies encompassing about 2000 cancer patients with central catheters [36]. Based on pooled estimates from four randomized studies, treatment with heparin (UFH or LMWH) resulted in a nonsignificant trend toward reduced risk of symptomatic VTE, with no difference in the rate of asymptomatic VTE, infection, or bleeding. Currently guidelines do not support use of thromboprophylaxis solely for prevention of catheter-associated thrombosis, largely based on marginal benefit and low event rates observed with newer studies [26].

4.6 Conclusions

The variation in risk for VTE between individual cancer patients is better understood with emerging data regarding clinical risk factors, D-dimers, and validated risk score, with several proposed and innovative modifications. We anticipate that future iterations of risk tools will take advantage of "-omics" data that is being steadily gathered for cancer patients from both cancer tissue and blood and are optimistic that such future risk tools will substantially improve on existing

sensitivity and specificity benchmarks. Given emerging data demonstrating benefit of thromboprophylaxis for cancer outpatients, ways to implement risk assessment and identification of patients who would benefit from prophylaxis are urgently needed. The goal of both risk assessment and thromboprophylaxis should be to reduce the overall burden and consequences of VTE in cancer, without adding to the clinical burden and complications suffered by patients.

References

1. Khorana AA (2010) Venous thromboembolism and prognosis in cancer. Thromb Res 125 (6):490–493
2. Khorana AA, Connolly GC (2009) Assessing risk of venous thromboembolism in the patient with cancer. J Clin Oncol 27(29):4839–4847
3. Khorana AA, Francis CW (2018, January 31) Risk prediction of cancer-associated thrombosis: appraising the first decade and developing the future. Thromb Res
4. Lau BD, Haut ER (2014) Practices to prevent venous thromboembolism: a brief review. BMJ Qual Saf 23(3):187–195
5. Chew HK, Wun T, Harvey D, Zhou H, White RH (2006) Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med 166(4):458–464
6. Blom JW, Doggen CJ, Osanto S, Rosendaal FR (2005) Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA 293(6):715–722
7. Chew HK, Davies AM, Wun T, Harvey D, Zhou H, White RH (2008) The incidence of venous thromboembolism among patients with primary lung cancer. J Thromb Haemost 6 (4):601–608
8. Agnelli G, Bolis G, Capussotti L, Scarpa RM, Tonelli F, Bonizzoni E et al (2006) A clinical outcome-based prospective study on venous thromboembolism after cancer surgery: the @RISTOS project. Ann Surg 243(1):89–95
9. Khorana AA, Francis CW, Culakova E, Lyman GH (2005) Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. Cancer 104(12):2822–2829
10. Fotopoulou C, duBois A, Karavas AN, Trappe R, Aminossadati B, Schmalfeldt B et al (2008) Incidence of venous thromboembolism in patients with ovarian cancer undergoing platinum/paclitaxel-containing first-line chemotherapy: an exploratory analysis by the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group. J Clin Oncol 26(16):2683–2689
11. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH (2007) Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. Cancer 110(10):2339–2346
12. Chen YW, Khorana AA (2017) The association between race and venous thromboembolism risk after initiation of chemotherapy: an analysis of the SAVE-ONCO trial control arm. Am J Hematol 92(6):E101–E103
13. Starling N, Rao S, Cunningham D, Iveson T, Nicolson M, Coxon F et al (2009) Thromboembolism in patients with advanced gastroesophageal cancer treated with anthracycline, platinum, and fluoropyrimidine combination chemotherapy: a report from the UK National Cancer Research Institute Upper Gastrointestinal Clinical Studies Group. J Clin Oncol 27(23):3786–3793
14. Scappaticci FA, Skillings JR, Holden SN, Gerber HP, Miller K, Kabbinavar F et al (2007) Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. J Natl Cancer Inst 99(16):1232–1239

15. Choueiri TK, Schutz FAB, Je Y, Rosenberg JE, Bellmunt J (2010) Risk of arterial thromboembolic events with sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials. JCO 28(13):2280–2285
16. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW (2008) Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 111 (10):4902–4907
17. Ay C, Vormittag R, Dunkler D et al (2009) D-dimer and prothrombin fragment 1 + 2 predict venous thromboembolism in patients with cancer: results from vienna cancer and thrombosis study. J Clin Oncol 27(25):4124–4129
18. Angelini D, Khorana AA (2017) Risk assessment scores for cancer-associated venous thromboembolic disease. Semin Thromb Hemost 43(5):469–478
19. Khorana AA (2018) Simplicity versus complexity: an existential dilemma as risk tools evolve. Lancet Hematol (in press)
20. Ay C, Dunkler D, Marosi C, Chiriac AL, Vormittag R, Simanek R et al (2010) Prediction of venous thromboembolism in cancer patients. Blood 116(24):5377–5382
21. Verso M, Agnelli G, Barni S, Gasparini G, LaBianca R (2012) A modified Khorana risk assessment score for venous thromboembolism in cancer patients receiving chemotherapy: the Protecht score. Intern Emerg Med 7(3):291–292
22. Cella CA, Di Minno G, Carlomagno C, Arcopinto M, Cerbone AM, Matano E et al (2017) Preventing venous thromboembolism in ambulatory cancer patients: the ONKOTEV study. Oncologist 22(5):601–608
23. Gerotziafas GT, Taher A, Abdel-Razeq H, AboElnazar E, Spyropoulos AC, El Shemmari S et al (2017) A predictive score for thrombosis associated with breast, colorectal, lung, or ovarian cancer: the prospective COMPASS-Cancer-Associated thrombosis study. Oncologist 22(10):1222–1231
24. Munoz Martin AJ, Ortega I, Font C, Pachon V, Castellon V, Martinez-Marin V et al (2018) Multivariable clinical-genetic risk model for predicting venous thromboembolic events in patients with cancer. Br J Cancer 118(8):1056–1061
25. Pabinger I, Van Es N, Heinze G, Posch F, Riedl J, Reitter EM et al (2010) Development and validation of a clinical prediction model for cancer-associated venous thromboembolism in two independent prospective cohorts. Lancet Haematol
26. Lyman GH, Bohlke K, Khorana AA, Kuderer NM, Lee AY, Arcelus JI et al (2007) Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of clinical oncology clinical practice guideline Update 2014. JCO 33(6):654–656
27. Khorana AA (2007) The NCCN clinical practice guidelines on venous thromboembolic disease: strategies for improving VTE prophylaxis in hospitalized cancer patients. Oncologist 12(11):1361–1370
28. Di Nisio MM, Carrier GH, Lyman AA (2014) Khorana and for the Subcommittee on Haemostasis and Malignancy. Prevention of venous thromboembolism in hospitalized medical cancer patients: guidance from the SSC of the ISTH. J Throm Haemost 12: 1746–1749
29. Samama MM, Cohen AT, Darmon J, Desjardins L, Eldor A, Janbon C et al (1999) A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. N Engl J Med 341(11):793–800
30. Agnelli G, George DJ, Kakkar AK, Fisher W, Lassen MR, Mismetti P et al (2012) Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. N Engl J Med 366(7):601–609
31. Hogg K, Carrier M (2012) Prevention and treatment of venous thromboembolism in patients with cancer. Therapeutic Adv Hematol 3(1):45–58
32. Khorana AA, Francis CW, Kuderer NM, Carrier M, Ortel TL, Wun T et al (2017) Dalteparin thromboprophylaxis in cancer patients at high risk for venous thromboembolism: a randomized trial. Thromb Res 151:89–95

33. Khorana AA, Soff GA, Kakkar AK, Vadhan-Raj S, Riess H, Wun T et al (2018) Rivaroxaban thromboprophylaxis in high-risk ambulatory cancer patients receiving systemic therapy: results of a randomized clinical trial (CASSINI). Blood 132(Suppl 1). LBA-1. Accessed December 27, 2018. https://doi.org/10.1182/blood-2018-120738
34. Carrier M, Abou-Nassar K, Mallick R, Tagalakis V, Shivakumar S, Schattner A, Kuruvilla P, Hill D, Spadafora S, Marquis K, Trinkaus M (2018) Apixaban to prevent venous thromboembolism in patients with cancer. New England J Med
35. Levine MN, Gu C, Liebman HA, Escalante CP, Solymoss S, Deitchman D et al (2012) A randomized phase II trial of apixaban for the prevention of thromboembolism in patients with metastatic cancer. J Thromb Haemost 10(5):807–814
36. Akl EA, Kamath G, Yosuico V, Kim SY, Barba M, Sperati F et al (2008) Thromboprophylaxis for patients with cancer and central venous catheters: a systematic review and a meta-analysis. Cancer 112(11):2483–2492

Biomarkers of Cancer-Associated Thromboembolism

5

Anjlee Mahajan and Ted Wun

Contents

A. Mahajan (✉) · T. Wun
Division of Hematology and Oncology, UC Davis School of Medicine, UC Davis Cancer Center, 4501 X Street, Sacramento, CA 95817, USA
e-mail: anmahajan@ucdavis.edu

T. Wun
UC Davis School of Medicine, Clinical and Translational Sciences Center (CTSC), Sacramento, USA

G. Soff (ed.), *Thrombosis and Hemostasis in Cancer*, Cancer Treatment and Research 179, https://doi.org/10.1007/978-3-030-20315-3_5

5.1 Overview

Cancer patients are known to be at increased risk of venous thromboembolism (VTE) as compared to the general population. In the nineteenth century, Armand Trousseau first reported the association between gastric cancer and thrombosis. Up to 20–30% of all VTE events are thought to be cancer associated [1]. Multiple studies have shown cancer-associated VTE (CAT) is associated with increased morbidity and mortality in patients [2–8]. The compromised survival of patients with CAT is present even when adjusting for co-morbidities and tumor stage, and as such venous thromboembolism is an independent risk factor for mortality [2].

In one prospective study, 8% of the cancer patients developed a venous thromboembolism within one year after diagnosis of their malignancy or progression of the disease [9]. In a study linking databases in the UK, the incidence rate of VTE in all cancers was 13.9 per 1000 person-years [10]. Among high-risk patients (with metastatic disease, high-grade tumors or treatment that increased VTE risk), the overall incidence rate was 68 per 1000 person-years (95% CI: 48–96) [11]. The incidence of VTE in cancer patients has continued to increase over time [12, 13]. This may be due to increased detection by serial scanning, change in treatments which may be more thrombogenic, and the fact that many cancer patients now have improved survival, increasing the time at risk [1].

There are likely multiple mechanisms for cancer-associated VTE, many of which are not well understood. In the nineteenth century, Virchow described the combination of stasis of blood flow, endothelial disruption, and hypercoagulability of blood as the risks for thrombosis, now commonly referred to as "Virchow's Triad." [14]. Initiation of coagulation is known to occur when tissue factor and factor VIIa come together to activate factor X via the extrinsic pathway. Tissue factor can occur in two forms, one in microparticles and the other form are expressed by platelets, leukocytes, and endothelial cells [15–17]. Tissue factor expressing microparticles have been found to be increased in patients with cancer and associated with increased risk of CAT [18]. Studies have suggested that malignant cells may also produce proteases, which directly cleave factor X to activate factor Xa [19, 20]. As part of the common pathway activated factor Xa then combines with factor V to convert prothrombin to thrombin.

C reactive protein (CRP) induces tissue factor expression from monocytes and endothelial cells [21–23] and is often elevated in inflammatory states, including cancer. CRP can also promote cellular P-selectin production, which mediates cell–cell interactions [21, 24]. Microparticles can also express P-selectin glycoprotein ligand 1 (PSGL-1) which allows them to bind P-selectin on the surface of endothelial cells, this then further propagates thrombosis formation [25, 26]. Platelets use glycoprotein Ib and IIb/IIIa for binding and adhesion, and tumor cells can also express these ligands [19, 27] and use them to initiate coagulation. Malignant cells are also known to inhibit fibrinolytic pathways. Plasminogen activator

Table 5.1 Common biomarkers for cancer-associated thrombosis and proposed mechanism

Biomarker	Proposed mechanism	References
CRP	Levels rise in response to inflammation, activates compliment	[21, 24, 31]
TF MP	TF MPs activate platelets and coagulation system	[36–42, 45–49]
D-dimer	Fibrin degradation product often used to predict VTE due to strong negative predictive value	[52]
P-selectin	Cell adhesion molecule which enhances release of TF MP	[59, 60]
PAI-1	Inhibits plasminogen and fibrinolysis	[61]
Factor VIII	Levels rise with inflammation, works to form thrombin through intrinsic coagulation pathway	[9]
Platelets	Adhere to damaged endothelium, aggregate and then activate the coagulation system	[68, 70, 71]
Leukocytes	Neutrophils activate thrombotic pathways by generating NETs; Monocytes express TF	[79–82]

Abbreviations: *CRP* C reactive protein; *TF MP* Tissue Factor Containing Microparticles; *PAI-1* Plasminogen Activator Inhibitor 1; *NET* Neutrophil Extracellular Traps

inhibitor 1(PAI-1), a serine protease inhibitor that functions as the inhibitor of tissue plasminogen activator and urokinase (i.e., fibrinolysis), has been detected in neoplastic cells [19, 20].

Understanding how cancer cells are able to manipulate and activate the physiologic coagulation system is key to improving our knowledge of cancer-associated thrombosis and how these phenomena may be prevented. Biomarkers such as C reactive protein, tissue factor, D-dimer, P-selectin, PAI-1, and factor VIII may all serve as clinically important molecules which can be measured to assess an individual's risk of thrombosis. In addition, studying the role of neutrophils and platelets in the activation of coagulation in patients with cancer may be beneficial in predicting the risk of cancer-associated thrombosis. Table 5.1 lists the common biomarkers for cancer-associated thrombosis covered in this chapter and the proposed mechanism. Many of the above-mentioned biomarkers are also known to increase with other inflammatory conditions besides cancer and can be elevated in the setting of infection as well, making specificity an issue.

The risk of venous thrombosis is dependent on multiple factors including cancer type and stage, individual patient characteristics, laboratory values, and treatments. Different risk assessment tools have been created to predict incident CAT [28, 29]. These tools take into account tumor-related factors, cancer subtype, and baseline laboratory values. For example, the Khorana score uses the type of cancer, thrombocytosis, anemia, leukocytosis, and body mass index to stratify patients who are low to high risk of CAT while receiving systemic therapy. The Vienna Cancer and Thrombosis (CATS) Study expanded on the Khorana score by also incorporating two additional biomarkers, soluble P-selectin (sP-selectin) and D-dimer [29].

Composite risk assessment tools using multiple different clinical and laboratory parameters are likely to be the key to enhancing predictive value.

5.2 Biomarkers to Predict Incident VTE

5.2.1 C Reactive Protein

C reactive protein (CRP) is a non-specific maker of inflammation and can be induced in tumors by lymphocytes and monocytes. CRP acts as an activator of the complement system [21] and levels have been found to correlate with tumor mass, often decreasing after surgical resection of tumors [30]. In preliminary studies, CRP has been shown to have some promise as a biomarker for cancer-associated thrombosis [21, 31].

The Vienna Cancer and Thrombosis Study (CATS), as mentioned above, evaluated CRP as one of several laboratory biomarkers [21]. Patients with high CRP (greater than 1.8 mg/dL, the 75th percentile for the cohort) were found to have an increased risk of developing a VTE in the first 12 months after entry (11.7% vs. 4.9%, $p = 0.03$). However, when analyzed in a multivariate model (adjusted for chemotherapy, radiation, surgery, tumor stage, and sP-selectin levels) CRP was no longer an independent predictor of VTE. CRP and sP-selectin levels were not correlated with each other. Lung and pancreatic cancer patients were found to have the highest levels of CRP, whereas breast and prostate cancer patients had the lowest levels. Kaplan–Meier analyses showed patients with an elevated baseline CRP level had significantly decreased 6- and 12-month survival rates (66 and 43%, respectively, vs. 90 and 82%, respectively), and this reduced survival was consistent across all tumor subtypes. In addition, as a continuous variable, CRP was associated with a HR of 1.3 (95% CI 1.2–1.3, $P < 0.0001$) for overall mortality, and this persisted after adjusting for age, gender, BMI, sP-selectin levels, and distant metastases. This study suggests that although CRP may not be an independent biomarker to predict VTE development, it may be predictive of mortality in patients with cancer.

5.2.2 Tissue Factor Expressing Microparticles (TF MP)

Tissue factor is a transmembrane receptor for factor VII/VIIa, and once the endothelial barrier is disrupted, exposure of extravascular TF leads to rapid activation of the extrinsic pathway of the clotting cascade. Tissue factor (TF) is expressed on tumor cells and expression has been shown to increase with histologic grade [32]. Microparticles (MP) are small membrane vesicles (≤ 1 μm) that are released from normal cells during activation or apoptosis and may also be released

by tumor cells [33]. In vitro studies have shown tissue factor microparticles (TF MP) to have procoagulant activity by facilitating the assembly of different coagulation factor complexes [34]. Previous studies have shown in vitro that tissue factor bearing microparticles from human breast [35] and pancreatic adenocarcinoma cells trigger the activation of coagulation and platelets by generating thrombin [36].

Injection of exogenous TF MP derived from human and mouse pancreatic cancer cells activates coagulation and increases thrombosis in different mouse models [36–39], however, the relevance in humans remains uncertain. Studies have examined thrombosis in a xenograft mouse model with human pancreatic cell lines expressing high TF [36, 38]. A recent study by Geddings et al. using human pancreatic adenocarcinoma cell lines showed TF-MP-activated human platelets and induced aggregation in vitro in a TF and thrombin-dependent manner [36]. Another study using mouse models showed inhibition of human TF significantly reduced clot size in tumor-bearing mice compared to mice in the control arm [40]. Taken together this research suggests that TF is responsible for increased clot size in tumor-bearing mice and may contribute to VTE in patients with pancreatic cancer.

While circulating TF-bearing MPs have been detected in patients with a variety of malignancies [41], pancreatic adenocarcinoma has been associated with the highest reported levels [42]. An explanation for these high levels of TF MP in pancreatic cancer patients may be related to the endocrine function of the pancreas, which allows for transport of MP into the bloodstream [43]. Because of the high levels of TF MP, this particular biomarker may be particularly useful in patients with pancreatic malignancy. TF MP has also been extensively studied in glioblastoma multiforme (GBM), another malignancy associated with a high rate of venous thrombosis, and different levels of expression have been found among different glioma subtypes [44].

There have been many prospective studies in humans examining the relationship between TF MP and VTE with different results. Thaler et al. performed a prospective cohort study to determine whether elevated TF MP activity at study entry was predictive of VTE in four cancer types (pancreatic, gastric, colorectal, and brain) [45]. Patients were followed for 24 months for the development of symptomatic VTE. Plasma TF MP activity was measured using a chromogenic endpoint and kinetic assays (in which TF-dependent factor Xa generation was quantified). Across all tumor types, there was no statistically significant association between TF MP activity and occurrence of VTE during follow up for either assay. Only in pancreatic patients was a borderline association between TF MP activity and increased risk of VTE found at the chromogenic endpoint assay [in a multivariable analysis hazard ratio (HR) 1.5, 95% CI 1–2.4, $p = 0.051$].

In a case control study, Zwicker et al. showed that elevations in plasma TF MP (as measured by flow cytometry) were associated with a near fourfold increase in VTE in ambulatory cancer patients (adjusted odds ratio, 3.72; 95% confidence interval, 1.18–11.76; $p = 0.01$) [46]. The same group then went on to perform a randomized phase II trial to evaluate the cumulative incidence of VTE in advanced cancer patients. They compared those with lower levels of TF MP not receiving thromboprophylaxis with low molecular weight heparin (LMWH) to those with

higher levels of circulating TF MP randomized to LMWH (Enoxaparin dose of 40 mg daily) or observation alone. Levels of TF MP were measured by flow cytometry and "high" levels were defined by reference repository of plasma from 60 cancer patients, using the top tercile from the reference specimens (3.5×10^4 microparticles/uL). The cumulative incidence of VTE (as diagnosed by bilateral lower extremity ultrasound at day 60) in the high TF MP group who received LMWH was 5.6% versus 27.3% in the high TF MP group who underwent observation alone (Gray test $p = 0.06$). The cumulative incidence of VTE in the low TF MP group was only 7.2% at day 60 [47]. The study was very promising but limited by the small size (70 patients), lack of power, and short follow-up. Ongoing TF MP research is limited by lack of consensus on the definition of tissue factor bearing microparticles and the different assays for measurement, which include both ELISA and flow-cytometry-based techniques [46–49].

5.2.3 D-Dimer (and F 1+2)

D-dimer is a fibrin degradation product that results from proteolytic cleavage of dimerized fibrin in a clot. It has clinical utility in diagnostic algorithms for venous thrombosis; as a normal (or low) value has high negative predictive value. However, the utility is limited in patients with underlying malignancy due to a lack of specificity, and patients with ongoing inflammation often have elevated levels [50, 51]. Ay et al. examined the utility of D-dimer and prothrombin fragment 1+2 (F 1+2), which reflect the activation of blood coagulation and fibrinolysis, to predict incident cancer-associated thrombosis [52]. Eight-hundred twenty-one patients were followed for a median of 500 days, and D-dimer and F 1+2 were determined. Baseline D-dimer and F 1+2 were significantly elevated in patients who developed a VTE, as opposed to those who did not (in a multivariate analysis, the hazard ratio (HR) for VTE in patients with elevated F 1+2 levels was 2.0; 95% CI, 1.2–3.6; $p = 0.015$). In addition, a twofold increase in D-dimer was associated with an increased risk of VTE (HR 1.3, 95% CI 1.2–1.6; $p < 0.001$), after adjusting for age, sex, surgery, chemotherapy, and radiation. The cumulative risk of developing VTE at six months was highest in patients with both elevated D-dimer and F 1+2 (15.2%) compared to those with normal levels (5%; $p < 0.001$).

Predicting cancer patients at risk for recurrent VTE, after an incident event, is also a clinical problem. D-dimer would be an interesting biomarker to investigate, as multiple models, including the Vienna Prediction Model and the DASH prediction rule, have shown D-dimer to be a useful predictor of VTE recurrence risk in the general population [53, 54]. Palereti et al. showed that patients with an abnormal D-dimer one month after discontinuing anticoagulation therapy had a significantly higher incidence of recurrent venous thromboembolism compared to those with a normal D-dimer level (HR 2.27; 95% CI, 1.15–4.46; $p = 0.02$) [55].

5.2.4 P-Selectin

P-selectin is a protein encoded by the SELP gene that functions as a cell adhesion molecule and is located on activated endothelial cells and platelets. P-selectin may also mediate cancer cell adhesion, inflammation, growth, and thrombosis [56–58]. P-selectin binds to P-selectin glycoprotein ligand-1 (PSGL-1) present on monocytes, which then results in tissue factor expression and the release of TF-bearing microparticles [59, 60].

The CATS study examined soluble P-selectin (sP-selectin) as biomarker for cancer-associated thrombosis [56]. Six hundred eighty-seven cancer patients were followed for a median of 415 days, and multiple cancer subtypes were included (solid tumors and hematologic malignancies). In a multivariable analysis elevated sP-selectin (above a cutoff level of 53.1 ng/mL, the 75th percentile of the study population) was a statistically significant risk factor for VTE after adjusting for age, sex, surgery, chemotherapy, and radiation (HR 2.6, 95% CI 1.4–4.9, $p = 0.003$). The cumulative probability of VTE six months after enrollment was 11.9% in patients with sP-selectin above the 75th percentile, and the authors concluded that high sP-selectin plasma levels independently predicted VTE in cancer patients.

5.2.5 PAI-1

Plasminogen activator inhibitor-1 (PAI-1) is a serine protease that functions to inhibit tissue plasminogen activator and urokinase, which are activators of plasminogen and fibrinolysis. Some research has suggested that patients with VTE have prolonged clot lysis times compared with healthy controls, and therefore concluded that elevated PAI-1 may contribute to diminished fibrinolytic activity [61]. There are limited studies, to date that examine the role of PAI-1 in cancer-associated thrombosis. One study showed higher levels of PAI-1 in patients with gliomas (compared to healthy controls) and another found that patients with pancreatic cancer may have higher levels of PAI-1 antigen and activity [62, 63]. Interestingly, a study showed that treatment with bevacizumab, an antiangiogenic monoclonal antibody, significantly increased expression of PAI-1 in tumor and plasma with associated increased thrombi in mice [64]. Additionally, bevacizumab did not enhance venous thrombosis in PAI-1 deficient mice, which suggested that PAI-1 may mediate the prothrombotic effect of bevacizumab.

5.2.6 Factor VIII

Factor VIII is produced liver sinusoidal cells and endothelial cells and circulates in the blood bound to von Willebrand factor multimers. It mediates coagulation through the intrinsic pathway, which activates Factor X leading to thrombin formation. Elevated factor VIII is often present in inflammatory states and has been shown to be elevated in certain malignancies [9, 65–67].

In an observational study using the Vienna CATS cohort, the cumulative probability of VTE after six months in 840 patients was 14% in those with an elevated Factor VIII, compared to 4% in those with normal levels ($p = 0.001$) [9]. The association was strongest in younger patients and declined with increasing age: a 20% increase in FVIII resulted in a twofold increased risk of VTE in forty-year-old subjects (95% CI 1.5–2.7, $p < 0.0001$), but only a 1.4-fold increased risk of VTE in 60-year-old patients (95% CI 1.2–1.6, $p < 0.00001$).

5.2.7 Platelets

Thrombocytosis is often observed in patients with malignancy, particularly of gastrointestinal, breast, lung, and ovarian origin [68]. While platelets are known to mediate the formation of arterial thrombosis, they also contribute to the initiation of venous thrombosis [69].

In pre-clinical models, clopidogrel (an inhibitor of adenosine diphosphate to the P2Y12 receptor on platelets) reduced binding of tumor-derived microparticles to the site of thrombus [70]. Other studies have shown that TF MP activate platelets, through increased thrombin production. This initiation of thrombosis in mice (by injection of TF MP) was also reduced by clopidogrel [36]. This suggests platelet inhibitors may be useful in preventing VTE in some cancer patients. Indeed, aspirin appears to be efficacious in the prevention of lenalidomide-associated VTE in patients with multiple myeloma [71]. Studies in ovarian cancer patients have also showed a reduction in VTE with use of aspirin, though this was not replicated for patients with breast cancer [72, 73].

As a biomarker, there has been some exploration of pre-treatment platelet counts to predict cancer-associated thrombosis. Khorana et al. performed an observational study of over 3000 patients who had received at least one cycle of chemotherapy to investigate the relationship between thrombocytosis and VTE development [74]. A pre-treatment platelet count of $>350 \times 10^9$/L was associated with a significantly higher risk of VTE (adjusted OR 2.81, 95% CI 1.63–4.93, $p = 0.0002$). Pre-chemotherapy platelet count, in addition to cancer site, anemia (hemoglobin of <10 g/dL), body mass index (BMI), and leukocyte count are all now incorporated into the Khorana Risk Score [28].

The Vienna CATS study also determined the utility of pre-chemotherapy platelet count in the prediction of cancer-associated thrombosis [75]. In an adjusted multivariate analysis, for every incremental increase in platelet count by $50 \times 10^9/mm^3$, the hazard ratio for VTE increased by 1.3 (95% CI 1.12–1.46; $p = 0.0003$). The authors also found that for platelet counts greater than 443×10^9/L (the 95th percentile for the cohort) the hazard ratio for VTE development was 3.5 (CI 1.5–8.1, $p = 0.003$).

5.2.8 Leukocytes

Neutrophils may contribute to the activation of thrombotic pathways by generating neutrophil extracellular traps (NETs) [76]. Pre-clinical studies have also shown that leukocytes contribute to venous thromboembolism by forming NETs [77, 78]. NETs are thought to help capture microvesicles and platelets, which then stabilize the thrombus. NETs also increase tissue factor activity [79–81]. In addition, activated monocytes express tissue factor. In mouse mammary carcinoma models, neutrophilia is found and thought to be mediated by increased granulocyte colony-stimulating factor [82, 83]. Thus, increased levels of cytokines that mediate hematopoiesis lead to leukocytosis, and neutrophilia in patients with cancer.

An elevated white blood cell count has been associated with an increased risk of VTE in cancer patients and is part of the Khorana Risk Score [28, 84]. In a multicenter observational study from 2010, data from 4000 patients with solid tumors and lymphomas was analyzed and leukocyte counts (prior to chemotherapy initiation and before each treatment cycle) were stratified in quartiles between 5.7 and 11 $\times$ 10^9/L [85]. Pre-chemotherapy leukocytosis was associated with a hazard ratio of 2.1 (95% CI 1.3–3.4, $p = 0.003$) for VTE (adjusted for malignancy type, stage, baseline platelet and hemoglobin count, BMI and use of erythropoietic stimulating agents). Patients with the highest absolute monocyte and neutrophil counts (as well as overall white blood cell count) had the highest rates of VTE. Leukocytosis remained an independent predictor of VTE after adjusting for concurrent thrombocytosis.

5.3 Biomarkers to Predict Recurrent VTE

While there have been many studies examining the pathophysiology and epidemiology of cancer-associated venous thromboembolism, most have focused on the incident VTE event. It is well known that patients with malignancy and venous thrombosis are at higher risk of VTE recurrence compared to those without cancer (HR = 3.2, 95% CI: 1.9–5.4) [86]. In a prospective study of patients receiving anticoagulation for VTE, those with active malignancy were found to have a significantly increased rate of recurrent VTE within a 12-month follow-up period compared to those without cancer [86]. In this same study, patients with lung and gastrointestinal (GI) cancers had a higher risk of recurrent VTE compared to other primary sites. The hazard ratio of recurrent thrombosis in lung cancer patients was 6.9 (95% CI: 3–15.9), and GI malignancy patients were 5.1 (95% CI: 2.3–11.3), compared with non-cancer controls. Breast cancer, in this cohort, was not associated with an increased risk of recurrent VTE. Accurate predictors of recurrent VTE in patients with, or without, malignancy remains elusive. In the Computerized Registry of Patients with Venous Thromboembolism (REITE registry), predictive variables for recurrent VTE included younger age (<65yo), clinically overt

pulmonary embolism (PE) as the initial presentation of VTE, or diagnosis of cancer within three months of VTE presentation [87].

The CATCH trial was a large, internationally randomized controlled trial comparing the use of tinzaparin versus warfarin for the treatment of acute symptomatic PE and/or DVT in patients with malignancy [88]. Thirty-one patients (6.9%) in the tinzaparin group and 45 patients (10%) in the warfarin group developed recurrent VTE during the 6-month follow-up period. Only hepatobiliary cancer, and venous compression secondary to tumor bulk or adenopathy, were found to be significantly associated with recurrent VTE. The authors recently published an analysis of the patients included in the CATCH cohort and examined CRP, D-dimer, Factor VIII, Tissue factor (TF) as measured by ELISA, and soluble P-selectin levels as predictors of the risk of VTE recurrence over a 6-month follow-up period [48]. Tissue factor levels in the highest quartile (>64.6 pg/mL; RR 3.3, 95% CI 2.1–5.1, $p < 0.0001$), and CRP levels >75 mg/L (RR 2.4, 95% CI 1.3–4.2, $p = 0.007$) were found to be associated with recurrent VTE, although on regression analysis only TF levels remained significantly associated with recurrent VTE (HR 3.4, 95% CI 2.1–5.5, $p < 0.001$). Elevated baseline (at the time of incident VTE) D-dimer, FVIII and sP-selectin were not associated with increased risk for recurrent VTE in this study.

A recent prospective study by van Es et al. [89] measured D-dimer and sP-selectin levels at 1, 4, 5, 12, and 24 weeks post-treatment initiation in patients with active cancer, and VTE receiving anticoagulation with low molecular weight heparin [89]. One-hundred seventeen patients were enrolled, and the authors found that baseline sP-selectin levels, but not D-dimer levels, were significantly associated with a higher risk of VTE recurrence. Interval biomarker levels during treatment were not associated with a higher risk of recurrent VTE.

The REITE (Computerized Registry of Patients with Venous Thromboembolism) database examined the white blood cell count at time of incident cancer-associated VTE and then again if a recurrent VTE occurred at 3-month follow-up [87]. Those patients with a white blood cell count of greater than 11×10^9/L were found to have a significant increase in recurrent thrombotic events (OR 1.6) and death (OR 2.7).

Some studies have suggested that the presence of residual thrombus after anticoagulation, particularly for patients with lower extremity DVT, increased the risk of recurrent VTE [86, 90, 91]. Young et al. examined 316 patients with DVT; they were stratified based on the complete resolution of thrombus (45%) versus those with residual thrombus (55%) after the completion of anticoagulation (which ranged from 3 to 6 months after the initial VTE event depending on the location of thrombus) [90]. Patients with residual thrombus on ultrasound were at higher risk of recurrence (HR = 2.2, 95% CI 1.19–4.21, $p = 0.012$), which remained significant after multivariable adjustment for age, gender, and cancer type.

In another study, 38 patients with cancer were serially monitored (at months 1, 3, 6 and 12) with compression ultrasound (CUS) after a first symptomatic DVT episode [92]. In this study, the absence of CUS normalization was the only predictor of recurrent thrombosis occurring at 3 and 6 months from the index DVT. Napolitano and colleagues evaluated the role of residual vein thrombosis to assess the optimal

duration of anticoagulant in patients with cancer who had lower extremity DVTs [93]. Three-hundred forty-seven patients were included. After initial anticoagulation for six months with LMWH, those with residual vein thrombosis (RVT) were randomly assigned to continue anticoagulation for six more months while those without RVT stopped anticoagulation. During a 12-month follow-up period, recurrent VTE occurred in only 3 of 105 patients without RVT compared to 22 of the 119 patients with RVT who received 12 total months of anticoagulation (HR 6, 95% CI: 1.7–21.2, $p = 0.005$). It remains unclear whether malignancy itself is a risk factor for residual venous thrombosis, or if residual thrombosis in patients with underlying malignancy is truly biomarker for recurrence.

5.4 Risk Assessment Models for CAT

The clinical relevance of studying biomarkers in cancer-associated thrombosis is to incorporate them into a decision tool that clinicians can use to help guide antithrombotic prophylaxis (primary and secondary) and therapy. As previously noted, Khorana et al. stratified cancer patients undergoing chemotherapy into different risk categories based on primary care site, pre-chemotherapy leukocyte count $>11 \times 10^9$/L, platelet count $>350 \times 10^9$/L, BMI >35 kg/m^2, and hemoglobin <10 gm/dL or use of erythropoietic stimulating agents [28]. Primary cancer sites were classified as "very high risk" (gastric and pancreatic cancer), "high risk" (lung, lymphoma, genitourinary excluding prostate, and gynecologic), and "average risk" (breast, colorectal, and prostate cancer). Risk of VTE was then divided into low risk (score = 0), intermediate (score 1–2), and high risk (score $\geq$ 3). Rates of VTE in the validation cohort were 0.3% (low risk), 2% (intermediate risk), and 6.7% (high risk) groups over a median time period of 2.5 months. This model is meant to identify those with a short-term risk of symptomatic VTE and was externally validated by the Vienna CATS consortium and other retrospective cohort studies [29, 94].

Table 5.2 Ottawa score for recurrent VTE risk in cancer-associated thrombosis [95]

Variable	Points
Female	1
Lung cancer	1
Breast cancer	−1
TNM stage 1	−2
Previous VTE	1

Adapted from Louzada et al. [95]. Patients with a score ≤ 0 had low risk ($\leq 4.5\%$) for recurrence and patients with a score >1 had a high risk ($\geq 19\%$) for VTE recurrence

As an extension of the Khorana score, the Vienna CATS consortium also incorporated the laboratory biomarkers sP-selectin and D-dimer [29]. The investigators showed that the incorporation of these two biomarkers resulted in more precise risk prediction. The follow-up time was also longer in this study (21 months vs. 2.5 months) than the original Khorana study, and the subsequent overall VTE rates were higher (7.4% vs. 2.1% in the derivation study for the Khorana score). The Vienna CATS study included a higher proportion of patients with high-risk cancer sites such as brain, gastric, and pancreatic tumors. However, a disadvantage of the Vienna risk model is that soluble P-selectin levels are not available in the routine clinical setting.

A risk model for the recurrence of cancer-associated thrombosis is the Ottawa Score, which was derived from a retrospective cohort of 543 cancer patients with PE or proximal DVT [95]. Female gender and type of cancer were independent predictors of recurrence in a multivariable model, although the final model also included prior history of VTE and cancer stage. In this model, the total score ranged between −3 and 3 points (Table 5.2). Patients with a score ≤ 0 had low risk ($\leq 4.5\%$) for VTE recurrence and patients with a score ≥ 1 had a high risk ($\geq 19\%$) of recurrence. The Ottawa score was subsequently validated after applying it to patients from the CLOT and CANTHANOX trials [96, 97].

5.5 Future Directions

There are many factors associated with the increased risk of VTE in patients with underlying malignancy. The above-mentioned biomarkers and pathways likely act synergistically to activate the coagulation system in vivo. To date, hospitalized and surgical patients with malignancy have been targeted for primary pharmacologic prophylaxis, however, the utility of providing the primary prophylaxis to ambulatory cancer patients receiving therapy remains unclear. Tumor subtype, extent of malignancy, underlying patient characteristics and treatment contribute to overall VTE risk. While most of these variables are incorporated into current risk models, identifying new easily measurable and analytically robust biomarkers remains an important goal to enhance risk assessment tools, and guide clinical decision making. As cancer-associated thrombosis is associated with increased morbidity and mortality, continued research into the development of predictive biomarkers may lead to improved survival and quality of life for patients with malignancy.

References

1. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC (2013) Epidemiology of cancer-associated venous thrombosis. Blood 122(10):1712–1723
2. Chew HK, Wun T, Harvey D, Zhou H, White RH (2006) Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med 166(4):458–464

3. Khorana AA, Liebman H, White R, Wun T, Lyman G (2008) The risk of venous thromboembolism in patients with cancer. American Society of Clinical Oncology educational book, pp 240–248
4. Chew HK, Wun T, Harvey DJ, Zhou H, White RH (2007) Incidence of venous thromboembolism and the impact on survival in breast cancer patients. J Clin Oncol 25 (1):70–76
5. Alcalay A, Wun T, Khatri V, Chew HK, Harvey D, Zhou H et al (2006) Venous thromboembolism in patients with colorectal cancer: incidence and effect on survival. J Clin Oncol 24(7):1112–1118
6. Sorensen HT, Mellemkjaer L, Olsen JH, Baron JA (2000) Prognosis of cancers associated with venous thromboembolism. N Engl J Med 343(25):1846–1850
7. Prandoni P, Falanga A, Piccioli A (2005) Cancer and venous thromboembolism. Lancet Oncol 6(6):401–410
8. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH (2007) Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost 5(3):632–634
9. Vormittag R, Simanek R, Ay C, Dunkler D, Quehenberger P, Marosi C et al (2009) High factor VIII levels independently predict venous thromboembolism in cancer patients: the cancer and thrombosis study. Arterioscler Thromb Vasc Biol 29(12):2176–2181
10. Walker AJ, Card TR, West J, Crooks C, Grainge MJ (2013) Incidence of venous thromboembolism in patients with cancer—a cohort study using linked United Kingdom databases. Eur J Cancer 49(6):1404–1413
11. Horsted F, West J, Grainge MJ (2012) Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. PLoS Med 9(7):e1001275
12. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH (2007) Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. Cancer 110(10):2339–2346
13. Stein PD, Beemath A, Meyers FA, Skaf E, Sanchez J, Olson RE (2006) Incidence of venous thromboembolism in patients hospitalized with cancer. Am J Med 119(1):60–68
14. Virchow RLK (1856) "Thrombose und Embolie. Gefässentzündung und septische Infektion" GAzwMFaMVMS, 219–732. Translation in Matzdorff AC, Bell WR (1998) Thrombosis and embolie (1846-1856). Science History Publications, Canton, Massachusetts. ISBN 0-88135-113-X
15. Falati S, Liu Q, Gross P, Merrill-Skoloff G, Chou J, Vandendries E et al (2003) Accumulation of tissue factor into developing thrombi in vivo is dependent upon microparticle P-selectin glycoprotein ligand 1 and platelet P-selectin. J Exp Med 197(11):1585–1598
16. Muller I, Klocke A, Alex M, Kotzsch M, Luther T, Morgenstern E et al (2003) Intravascular tissue factor initiates coagulation via circulating microvesicles and platelets. FASEB J 17 (3):476–478
17. Bogdanov VY, Balasubramanian V, Hathcock J, Vele O, Lieb M, Nemerson Y (2003) Alternatively spliced human tissue factor: a circulating, soluble, thrombogenic protein. Nat Med 9(4):458–462
18. Zwicker JI (2008) Tissue factor-bearing microparticles and cancer. Semin Thromb Hemost 34 (2):195–198
19. Nijziel MR, van Oerle R, Hillen HF, Hamulyak K (2006) From trousseau to angiogenesis: the link between the haemostatic system and cancer. Neth J Med 64(11):403–410
20. Caine GJ, Stonelake PS, Lip GY, Kehoe ST (2002) The hypercoagulable state of malignancy: pathogenesis and current debate. Neoplasia 4(6):465–473
21. Kanz R, Vucokich T, Vormittag R, Dunkler D, Ay C, Thaler J, Haselbock K, Scheithauer W, Zielinksi C, Pabinger I (2011) Thrombosis risk and survival in cancer patients with elevated C-reactive protein. J Thromb Haemost 9(1):57–63
22. Cermak J, Key NS, Bach RR, Balla J, Jacob HS, Vercellotti GM (1993) C-reactive protein induces human peripheral blood monocytes to synthesize tissue factor. Blood 82(2):513–520

23. Cirillo P, Golino P, Calabro P, Cali G, Ragni M, De Rosa S et al (2005) C-reactive protein induces tissue factor expression and promotes smooth muscle and endothelial cell proliferation. Cardiovasc Res 68(1):47–55
24. Molins B, Pena E, Vilahur G, Mendieta C, Slevin M, Badimon L (2008) C-reactive protein isoforms differ in their effects on thrombus growth. Arterioscler Thromb Vasc Biol 28 (12):2239–2246
25. Lopez JA, Kearon C, Lee AY (2004) Deep venous thrombosis. Hematol Am Soc Hematol Educ Program 439–456
26. Pabinger I, Ay C (2009) Biomarkers and venous thromboembolism. Arterioscler Thromb Vasc Biol 29(3):332–336
27. Osborne NH, Wakefield TW, Henke PK (2008) Venous thromboembolism in cancer patients undergoing major surgery. Ann Surg Oncol 15(12):3567–3578
28. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW (2008) Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 111 (10):4902–4907
29. Ay C, Dunkler D, Marosi C, Chiriac AL, Vormittag R, Simanek R et al (2010) Prediction of venous thromboembolism in cancer patients. Blood 116(24):5377–5382
30. Devaraj S, Dasu MR, Singh U, Rao LV, Jialal I (2009) C-reactive protein stimulates superoxide anion release and tissue factor activity in vivo. Atherosclerosis 203(1):67–74
31. Kroger K, Weiland D, Ose C, Neumann N, Weiss S, Hirsch C et al (2006) Risk factors for venous thromboembolic events in cancer patients. Ann Oncol 17(2):297–303
32. Khorana AA, Ahrendt SA, Ryan CK, Francis CW, Hruban RH, Hu YC et al (2007) Tissue factor expression, angiogenesis, and thrombosis in pancreatic cancer. Clin Cancer Res 13 (10):2870–2875
33. Mackman N (2009) The many faces of tissue factor. J Thromb Haemost 7(Suppl 1):136–139
34. Gardiner C, Harrison P, Belting M, Boing A, Campello E, Carter BS et al (2015) Extracellular vesicles, tissue factor, cancer and thrombosis—discussion themes of the ISEV 2014 educational day. J Extracell Vesicles 4:26901
35. Davila M, Amirkhosravi A, Coll E, Desai H, Robles L, Colon J et al (2008) Tissue factor-bearing microparticles derived from tumor cells: impact on coagulation activation. J Thromb Haemost 6(9):1517–1524
36. Geddings JE, Hisada Y, Boulaftali Y, Getz TM, Whelihan M, Fuentes R et al (2016) Tissue factor-positive tumor microvesicles activate platelets and enhance thrombosis in mice. J Thromb Haemost 14(1):153–166
37. Thomas GM, Panicot-Dubois L, Lacroix R, Dignat-George F, Lombardo D, Dubois C (2009) Cancer cell-derived microparticles bearing P-selectin glycoprotein ligand 1 accelerate thrombus formation in vivo. J Exp Med 206(9):1913–1927
38. Wang JG, Geddings JE, Aleman MM, Cardenas JC, Chantrathammachart P, Williams JC et al (2012) Tumor-derived tissue factor activates coagulation and enhances thrombosis in a mouse xenograft model of human pancreatic cancer. Blood 119(23):5543–5552
39. Thomas GM, Brill A, Mezouar S, Crescence L, Gallant M, Dubois C et al (2015) Tissue factor expressed by circulating cancer cell-derived microparticles drastically increases the incidence of deep vein thrombosis in mice. J Thromb Haemost 13(7):1310–1319
40. Hisada Y, Ay C, Auriemma AC, Cooley BC, Mackman N (2017) Human pancreatic tumors grown in mice release tissue factor-positive microvesicles that increase venous clot size. J Thromb Haemost 15(11):2208–2217
41. Tesselaar ME, Romijn FP, van der Linden IK, Bertina RM, Osanto S (2009) Microparticle-associated tissue factor activity in cancer patients with and without thrombosis. J Thromb Haemost 7(8):1421–1423
42. Geddings JE, Mackman N (2013) Tumor-derived tissue factor-positive microparticles and venous thrombosis in cancer patients. Blood 122(11):1873–1880
43. Hisada Y, Mackman N (2017) Cancer-associated pathways and biomarkers of venous thrombosis. Blood 130(13):1499–1506

44. Magnus N, Gerges N, Jabado N, Rak J (2013) Coagulation-related gene expression profile in glioblastoma is defined by molecular disease subtype. J Thromb Haemost 11(6):1197–1200
45. Thaler J, Ay C, Mackman N, Bertina RM, Kaider A, Marosi C et al (2012) Microparticle-associated tissue factor activity, venous thromboembolism and mortality in pancreatic, gastric, colorectal and brain cancer patients. J Thromb Haemost 10(7):1363–1370
46. Zwicker JI, Liebman HA, Neuberg D, Lacroix R, Bauer KA, Furie BC et al (2009) Tumor-derived tissue factor-bearing microparticles are associated with venous thromboembolic events in malignancy. Clin Cancer Res 15(22):6830–6840
47. Zwicker JI, Liebman HA, Bauer KA, Caughey T, Campigotto F, Rosovsky R et al (2013) Prediction and prevention of thromboembolic events with enoxaparin in cancer patients with elevated tissue factor-bearing microparticles: a randomized-controlled phase II trial (the microtec study). Br J Haematol 160(4):530–537
48. Khorana AA, Kamphuisen PW, Meyer G, Bauersachs R, Janas MS, Jarner MF et al (2017) Tissue factor as a predictor of recurrent venous thromboembolism in malignancy: biomarker analyses of the CATCH trial. J Clin Oncol 35(10):1078–1085
49. Tesselaar ME, Romijn FP, Van Der Linden IK, Prins FA, Bertina RM, Osanto S (2007) Microparticle-associated tissue factor activity: a link between cancer and thrombosis? J Thromb Haemost 5(3):520–527
50. Kohli M, Fink LM, Spencer HJ, Zent CS (2002) Advanced prostate cancer activates coagulation: a controlled study of activation markers of coagulation in ambulatory patients with localized and advanced prostate cancer. Blood Coagul Fibrinolysis 13(1):1–5
51. Hanzal E, Tatra G (1993) Prothrombin fragment F 1+2 plasma concentrations in patients with gynecologic malignancies. Gynecol Oncol 49(3):373–376
52. Ay C, Vormittag R, Dunkler D, Simanek R, Chiriac AL, Drach J et al (2009) D-dimer and prothrombin fragment 1+2 predict venous thromboembolism in patients with cancer: results from the Vienna Cancer and Thrombosis study. J Clin Oncol 27(25):4124–4129
53. Eichinger S, Heinze G, Jandeck LM, Kyrle PA (2010) Risk assessment of recurrence in patients with unprovoked deep vein thrombosis or pulmonary embolism: the Vienna prediction model. Circulation 121(14):1630–1636
54. Tosetto A, Iorio A, Marcucci M, Baglin T, Cushman M, Eichinger S et al (2012) Predicting disease recurrence in patients with previous unprovoked venous thromboembolism: a proposed prediction score (DASH). J Thromb Haemost 10(6):1019–1025
55. Palareti G, Cosmi B, Legnani C, Tosetto A, Brusi C, Iorio A et al (2006) D-dimer testing to determine the duration of anticoagulation therapy. N Engl J Med 355(17):1780–1789
56. Ay C, Simanek R, Vormittag R, Dunkler D, Alguel G, Koder S et al (2008) High plasma levels of soluble P-selectin are predictive of venous thromboembolism in cancer patients: results from the Vienna Cancer and Thrombosis Study (CATS). Blood 112(7):2703–2708
57. Chen M, Geng JG (2006) P-selectin mediates adhesion of leukocytes, platelets, and cancer cells in inflammation, thrombosis, and cancer growth and metastasis. Arch Immunol Ther Exp (Warsz) 54(2):75–84
58. Geng JG, Chen M, Chou KC (2004) P-selectin cell adhesion molecule in inflammation, thrombosis, cancer growth and metastasis. Curr Med Chem 11(16):2153–2160
59. Cambien B, Wagner DD (2004) A new role in hemostasis for the adhesion receptor P-selectin. Trends Mol Med 10(4):179–186
60. Furie B, Furie BC (2004) Role of platelet P-selectin and microparticle PSGL-1 in thrombus formation. Trends Mol Med 10(4):171–178
61. Meltzer ME, Lisman T, de Groot PG, Meijers JC, le Cessie S, Doggen CJ et al (2010) Venous thrombosis risk associated with plasma hypofibrinolysis is explained by elevated plasma levels of TAFI and PAI-1. Blood 116(1):113–121
62. Andren-Sandberg A, Lecander I, Martinsson G, Astedt B (1992) Peaks in plasma plasminogen activator inhibitor-1 concentration may explain thrombotic events in cases of pancreatic carcinoma. Cancer 69(12):2884–2887

63. Sciacca FL, Ciusani E, Silvani A, Corsini E, Frigerio S, Pogliani S et al (2004) Genetic and plasma markers of venous thromboembolism in patients with high grade glioma. Clin Cancer Res 10(4):1312–1317
64. Chen N, Ren M, Li R, Deng X, Li Y, Yan K et al (2015) Bevacizumab promotes venous thromboembolism through the induction of PAI-1 in a mouse xenograft model of human lung carcinoma. Mol Cancer 14:140
65. Yigit E, Gonullu G, Yucel I, Turgut M, Erdem D, Cakar B (2008) Relation between hemostatic parameters and prognostic/predictive factors in breast cancer. Eur J Intern Med 19 (8):602–607
66. Battistelli S, Stefanoni M, Lorenzi B, Dell'avanzato R, Varrone F, Pascucci A et al (2008) Coagulation factor levels in non-metastatic colorectal cancer patients. Int J Biol Markers 23 (1):36–41
67. Minnema MC, Fijnheer R, De Groot PG, Lokhorst HM (2003) Extremely high levels of von Willebrand factor antigen and of procoagulant factor VIII found in multiple myeloma patients are associated with activity status but not with thalidomide treatment. J Thromb Haemost 1 (3):445–449
68. Levin J, Conley CL (1964) Thrombocytosis associated with malignant disease. Arch Intern Med 114:497–500
69. Connolly GC, Phipps RP, Francis CW (2014) Platelets and cancer-associated thrombosis. Semin Oncol 41(3):302–310
70. Mezouar S, Darbousset R, Dignat-George F, Panicot-Dubois L, Dubois C (2015) Inhibition of platelet activation prevents the P-selectin and integrin-dependent accumulation of cancer cell microparticles and reduces tumor growth and metastasis in vivo. Int J Cancer 136(2):462–475
71. Larocca A, Cavallo F, Bringhen S, Di Raimondo F, Falanga A, Evangelista A et al (2012) Aspirin or enoxaparin thromboprophylaxis for patients with newly diagnosed multiple myeloma treated with lenalidomide. Blood 119(4):933–939; quiz 1093
72. Shai A, Rennert HS, Lavie O, Ballan-Haj M, Bitterman A, Steiner M et al (2014) Statins, aspirin and risk of venous thromboembolic events in breast cancer patients. J Thromb Thrombolysis 38(1):32–38
73. Shai A, Rennert HS, Rennert G, Sagi S, Leviov M, Lavie O (2014) Statins, aspirin and risk of thromboembolic events in ovarian cancer patients. Gynecol Oncol 133(2):304–308
74. Khorana AA, Francis CW, Culakova E, Lyman GH (2005) Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. Cancer 104(12):2822–2829
75. Simanek R, Vormittag R, Ay C, Alguel G, Dunkler D, Schwarzinger I et al (2010) High platelet count associated with venous thromboembolism in cancer patients: results from the Vienna Cancer and Thrombosis Study (CATS). J Thromb Haemost 8(1):114–120
76. Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS et al (2004) Neutrophil extracellular traps kill bacteria. Science 303(5663):1532–1535
77. Fuchs TA, Brill A, Duerschmied D, Schatzberg D, Monestier M, Myers DD Jr et al (2010) Extracellular DNA traps promote thrombosis. Proc Natl Acad Sci U S A 107(36):15880–15885
78. Brill A, Suidan GL, Wagner DD (2013) Hypoxia, such as encountered at high altitude, promotes deep vein thrombosis in mice. J Thromb Haemost 11(9):1773–1775
79. Demers M, Wagner DD (2013) Neutrophil extracellular traps: a new link to cancer-associated thrombosis and potential implications for tumor progression. Oncoimmunology 2(2):e22946
80. Demers M, Wong SL, Martinod K, Gallant M, Cabral JE, Wang Y et al (2016) Priming of neutrophils toward NETosis promotes tumor growth. Oncoimmunology 5(5):e1134073
81. Olsson AK, Cedervall J (2016) NETosis in cancer—platelet-neutrophil crosstalk promotes tumor-associated pathology. Front Immunol 7:373
82. Demers M, Krause DS, Schatzberg D, Martinod K, Voorhees JR, Fuchs TA et al (2012) Cancers predispose neutrophils to release extracellular DNA traps that contribute to cancer-associated thrombosis. Proc Natl Acad Sci U S A 109(32):13076–13081

83. Kowanetz M, Wu X, Lee J, Tan M, Hagenbeek T, Qu X et al (2010) Granulocyte-colony stimulating factor promotes lung metastasis through mobilization of Ly6G + Ly6C + granulocytes. Proc Natl Acad Sci U S A 107(50):21248–21255
84. Blix K, Jensvoll H, Braekkan SK, Hansen JB (2013) White blood cell count measured prior to cancer development is associated with future risk of venous thromboembolism–the tromso study. PLoS ONE 8(9):e73447
85. Connolly GC, Khorana AA, Kuderer NM, Culakova E, Francis CW, Lyman GH (2010) Leukocytosis, thrombosis and early mortality in cancer patients initiating chemotherapy. Thromb Res 126(2):113–118
86. Prandoni P, Lensing AW, Piccioli A, Bernardi E, Simioni P, Girolami B et al (2002) Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 100(10):3484–3488
87. Trujillo-Santos J, Prandoni P, Rivron-Guillot K, Roman P, Sanchez R, Tiberio G et al (2008) Clinical outcome in patients with venous thromboembolism and hidden cancer: findings from the RIETE registry. J Thromb Haemost 6(2):251–255
88. Lee AYY, Kamphuisen PW, Meyer G, Bauersachs R, Janas MS, Jarner MF et al (2015) Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. JAMA 314(7):677–686
89. van Es N, Louzada M, Carrier M, Tagalakis V, Gross PL, Shivakumar S et al (2018) Predicting the risk of recurrent venous thromboembolism in patients with cancer: a prospective cohort study. Thromb Res 163:41–46
90. Young L, Ockelford P, Milne D, Rolfe-Vyson V, McKelvie S, Harper P (2006) Post-treatment residual thrombus increases the risk of recurrent deep vein thrombosis and mortality. J Thromb Haemost 4(9):1919–1924
91. Mazetto BM, Orsi FLA, Silveira SAF, Bittar LF, Flores-Nascimento MMC, Zapponi KCS et al (2017) Residual vein thrombosis echogenicity is associated to the risk of DVT recurrence: a cohort study. Clin Appl Thromb Hemost 1076029617700997
92. Piovella F, Crippa L, Barone M, Vigano D'Angelo S, Serafini S, Galli L et al (2002) Normalization rates of compression ultrasonography in patients with a first episode of deep vein thrombosis of the lower limbs: association with recurrence and new thrombosis. Haematologica 87(5):515–522
93. Napolitano M, Saccullo G, Malato A, Sprini D, Ageno W, Imberti D et al (2014) Optimal duration of low molecular weight heparin for the treatment of cancer-related deep vein thrombosis: the cancer-DACUS study. J Clin Oncol 32(32):3607–3612
94. Khorana AA, Rubens D, Francis CW (2014) Screening high-risk cancer patients for VTE: a prospective observational study. Thromb Res 134(6):1205–1207
95. Louzada ML, Carrier M, Lazo-Langner A, Dao V, Kovacs MJ, Ramsay TO et al (2012) Development of a clinical prediction rule for risk stratification of recurrent venous thromboembolism in patients with cancer-associated venous thromboembolism. Circulation 126(4):448–454
96. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M et al (2003) Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 349(2):146–153
97. Meyer G, Marjanovic Z, Valcke J, Lorcerie B, Gruel Y, Solal-Celigny P et al (2002) Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. Arch Intern Med 162(15):1729–1735

Thrombotic Risk from Chemotherapy and Other Cancer Therapies

6

M. D. Debbie Jiang and M. D. Alfred Ian Lee

Contents

M. D. Debbie Jiang (✉) · M. D. Alfred Ian Lee
Department of Internal Medicine, Yale School of Medicine, New Haven, CT, USA
e-mail: dcjiang@uw.edu

M. D. Alfred Ian Lee
Yale School of Medicine, New Haven, CT, USA
e-mail: alfred.lee@yale.edu

G. Soff (ed.), *Thrombosis and Hemostasis in Cancer*, Cancer Treatment and Research 179, https://doi.org/10.1007/978-3-030-20315-3_6

6.1 Introduction

Cancer was first noted by Trousseau to be associated with thrombosis in the 1860s [1]. Compared to healthy counterparts, patients with active malignancy have a four- to sevenfold higher incidence of symptomatic venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), and a twofold increase in incidence of arterial thromboembolic events such as myocardial infarction and stroke [2, 3]. The absolute incidence of thrombosis in cancer patients ranges from <1% to almost 20% in database and prospective cohort studies [2, 4]. This wide range likely reflects the many contributing factors to thromboembolic risk, including type of malignancy, stage, treatment, underlying hypercoagulable disorders, surgical procedures, and use of central venous catheters.

Systemic cancer therapy is estimated to increase thromboembolic risk by six- to sevenfold, with an annual incidence of about 10–20% [2, 5–7]. The risk of chemotherapy-induced thrombosis is highest during the first few months after initiation of treatment; a retrospective observational cohort study of 17,284 patients with different types of solid tumor malignancies reported that 18% of VTE events occurred within 1 month of starting chemotherapy, while 73% of events occurred within the first 6 months [2]. The mechanisms by which cancer therapies lead to thrombosis are diverse and vary according to the specific type of agent used.

Tamoxifen and L-asparaginase were among the first cancer therapeutic agents described in association with thrombosis, during the 1970s [8, 9]. With time, other conventional cytotoxic chemotherapies also became recognized as independent risk factors for thrombosis [10, 11]. An increase in the rates of cancer thrombosis in the late 1990s through early 2000s was thought to be at least partly due to the use of drugs with antiangiogenic properties, e.g., bevacizumab or immunomodulatory imide drugs (IMiDs) [2, 12, 13]. This chapter discusses the thrombotic risks of different cancer therapies, the mechanisms by which such therapies modulate thrombosis risks, and how such risks may be appropriately managed.

6.2 Hormone Therapy

6.2.1 Selective Estrogen Receptor Modulators (SERMs)

Since its initial use as adjuvant therapy and chemoprevention for breast cancer, tamoxifen has been observed to increase the risk of VTE, with a relative risk of

two- to sevenfold in different studies [10, 11, 14, 15]. In two major randomized clinical trials of breast cancer prevention in high-risk women, the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 Study and the International Breast Cancer Intervention Study (IBIS-I), the relative risk of VTE with tamoxifen was 2.5–3 times greater than placebo [16, 17]. Similar effects were observed in the NSABP B-14 trial of adjuvant tamoxifen versus placebo, and in the NSABP B-20 trial of adjuvant tamoxifen plus chemotherapy versus tamoxifen or chemotherapy alone, following surgery for early-stage breast cancer [18, 19].

The incidence of tamoxifen-associated VTE is highest during the first 2 years after starting the drug and normalizes upon its discontinuation [6, 16, 20]. DVT is more common than PE, although the development of PE from tamoxifen use is linked to increased mortality [6, 16, 17]. The risk of tamoxifen-induced VTE is further amplified with menopause, advancing age, or major surgery [10, 14, 16]. Other risk factors include body mass index, cigarette smoking, traditional coronary artery risk factors such as hypertension and hypercholesterolemia, or a family history of coronary artery disease [21–23].

The presence of thrombophilia may augment the thrombotic risk of tamoxifen, although the literature is divided in this regard. In a case-control study from the Cancer and Leukemia Group B (CALGB), the presence of Factor V Leiden (FVL) significantly increased the risk of VTE from tamoxifen use [23]. Other studies either failed to demonstrate such an association or observed this only with FVL but not with other heritable thrombophilias [21, 24, 25]. The mechanism by which tamoxifen increases VTE risk is thought to be its estrogen agonist properties (which may also explain the possible association with FVL).

Tamoxifen's effect on arterial thrombosis is less well characterized. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of 21,457 patients receiving 5 years of adjuvant tamoxifen versus placebo noted a trend toward increased stroke death that was balanced by a similar trend toward decreased cardiac mortality [6]. The NSABP P-1 trial also showed a non-statistically significant increase in stroke risk with tamoxifen, while the IBIS-I trial did not. The reported decrease in myocardial infarction with tamoxifen in the EBCTCG trial has been observed in other studies as well, although the magnitude of this effect has generally been low [26].

Raloxifene, another SERM, has also been tied to thrombosis. In a multicenter randomized control trial comparing raloxifene to placebo for fracture prevention in patients with osteoporosis, raloxifene had a threefold increased risk of VTE [27]. A meta-analysis of 24,523 women enrolled on several clinical trials reported a 62% increase in VTE risk with raloxifene [28]. However, the thrombotic risk of raloxifene appears to be less than tamoxifen; in a head-to-head trial of raloxifene versus tamoxifen for primary prevention of breast cancer, VTE risk was 30% lower with raloxifene [29].

6.2.2 Aromatase Inhibitors

Aromatase inhibitors such as anastrozole and letrozole have not been associated with thrombosis. The MA.17 trial from the National Cancer Institute of Canada Clinical Trials Group, which studied adjuvant tamoxifen followed by either letrozole or placebo in 5170 patients with breast cancer, found no statistically significant increase in thrombotic events in the letrozole arm [30]. The arimidex, tamoxifen alone, or in combination trial of 9366 breast cancer patients reported similar risks of VTE in patients treated with tamoxifen with or without anastrozole, suggesting that thrombotic risk was attributed to tamoxifen and not anastrozole [31].

Approach to treatment: For women with a personal history of VTE or a known thrombophilia, or who are otherwise deemed to have a high risk of VTE, caution is advised with tamoxifen or raloxifene use, while aromatase inhibition is viewed as a safer option. Thrombophilia testing may be considered in the event of a family history of thrombosis, although the clinical implications of such findings are unclear. In women with a high risk of thrombosis who must take tamoxifen or raloxifene, prophylactic anticoagulation is advisable for the duration of therapy.

6.3 Immunomodulatory Drugs: Thalidomide, Lenalidomide, and Pomalidomide

On their own, the immunomodulatory imide drugs (IMiDs), thalidomide and its derivative and lenalidomide, have not been found to increase the risk of VTE. However, when used in combination with dexamethasone or cytotoxic chemotherapy in the treatment of multiple myeloma (MM), thrombosis risk increases enormously. The incidence of thrombosis in MM is less than 5% for thalidomide alone, versus 10–20% for thalidomide with dexamethasone and 20–40% for thalidomide with chemotherapy [14, 15, 32–34]. Similar effects have been observed with lenalidomide plus dexamethasone [34]. An increase in VTE risk has not been reported with pomalidomide in combination with dexamethasone, but this may be related to standardized use of thromboprophylaxis [35].

MM patients with newly diagnosed disease have a higher risk of VTE with thalidomide-containing drug regimens than those with relapsed disease [34, 36]. The use of erythropoiesis-stimulating agents (ESAs) also increases thrombotic risk in MM patients treated with thalidomide- or lenalidomide-containing regimens [37, 38]. Interestingly, the protease inhibitor bortezomib appears to have a protective effect against thrombosis from IMiDs in MM [39].

The risk of thrombosis in non-Hodgkin lymphoma patients treated with lenalidomide is similar to that in MM patients but is lower when lenalidomide is used in combination with biologic agents such as rituximab [40, 41]. By contrast, the risk of thrombosis in myelodysplastic syndrome (MDS) patients treated with lenalidomide is low [42].

The mechanism of thrombosis due to IMiDs in treatment of MM is thought to be multifactorial [15]. In vitro, cells treated with doxorubicin followed by thalidomide have enhanced expression of protease-activated receptor-1 (PAR-1), a G protein-coupled receptor expressed by platelets and endothelial cells that binds thrombin and participates in platelet activation and aggregation [43]; this effect is not observed in cells treated with either agent alone. Thalidomide also induces conformational changes in platelet glycoprotein IIb/IIIa ($\alpha_{IIb}\beta_3$) on platelet surfaces, which may further activate platelets [44]. In some patients on thalidomide, levels of procoagulant factors such as von Willebrand factor (vWF) or factor VIII may rise, while endogenous anticoagulants such as protein S, antithrombin, and thrombomodulin may decline [45]. One study found a decrease in thrombomodulin levels in thalidomide-treated MM patients, while another did not [46, 47]. In vitro and in MM patients, lenalidomide may decrease levels of PU.1, a transcription factor involved in granulocyte differentiation, resulting in accumulation of promyelocytes and an increase in cathepsin G, a platelet aggregation agonist that may lead to VTE [48]. Acquired activated protein C resistance and changes in tissue factor or vascular endothelial growth factor (VEGF) may also play a role [49, 50].

Genetics may underlie some of the observed thrombotic risk with IMiDs in MM. In one study, thalidomide-treated MM patients who developed VTE were more likely to have a heritable thrombophilia such as FVL, prothrombin gene mutation, or a deficiency in antithrombin or protein S [51]; another study of lenalidomide-induced VTE, however, found no such association [52]. A study of MM patients treated with thalidomide-containing regimens from three large clinical trials identified single-nucleotide polymorphisms (SNPs) involved in cytokine balance, DNA repair, and drug transport and metabolism in those who developed VTE [53]. Another study of lenalidomide-treated MM patients found that those with a particular SNP in transcription factor NKκB were more likely to develop VTE while on low-dose aspirin [52].

The protective mechanism of bortezomib against thrombosis in MM may be partly related to changes in platelet count or platelet aggregation, as observed in bortezomib-treated patients [54]. Bortezomib also inhibits transcription factor NF-κB, which in turn affects expression of plasminogen activator inhibitor-1, with potential effects on thrombomodulin or tissue factor [39].

The risk of VTE for MM patients receiving lenalidomide and dexamethasone drops from 11–27% down to 1–3% with thromboprophylaxis using aspirin or low-molecular-weight heparin (LMWH) [55]. The landmark GIMEMA study, a randomized controlled trial evaluating aspirin, warfarin, and LMWH prophylaxis in MM patients receiving thalidomide-based regimens, found no significant difference in VTE events overall except in elderly patients, where warfarin was inferior to LMWH and aspirin [56]. Expert reviews and consensus guidelines from the American Society of Clinical Oncology, the International Myeloma Working Group, and Europe recommend thromboprophylaxis with aspirin, LMWH, or warfarin for MM patients on IMiD-containing regimens [34, 35, 57, 58].

Approach to treatment: All MM patients who are treated with thalidomide, lenalidomide, or pomalidomide should receive thromboprophylaxis with aspirin, prophylactic-dose LMWH, or warfarin. For MM patients receiving single-agent thalidomide or lenalidomide in whom the risk of aspirin or other thromboprophylactic drugs is thought to outweigh the potential benefits, such thromboprophylaxis may be deferred. In MM patients receiving IMiDs with high-dose dexamethasone or with combination chemotherapy, LMWH or warfarin is favored over aspirin. For MM patients on IMiDs who develop VTE, full-dose anticoagulation should be continued for the duration of IMiD therapy.

6.4 Cytotoxic Chemotherapy

Conventional cytotoxic chemotherapy damages endothelial cells and causes apoptosis, which may lead to increased thrombin generation via tissue factor-dependent mechanisms [59, 60]. Certain chemotherapy agents may also reduce endogenous anticoagulant factors such as protein C and protein S and may alter intercellular interactions and platelet reactivity [14, 61].

6.4.1 Cisplatin

An association of cisplatin with thrombosis was first reported during the 1980s in treatment of testicular or ovarian cancer. A retrospective review comparing cisplatin-based and non-cisplatin-based chemotherapies in solid tumor malignancies and lymphoma reported a threefold increase in VTE among patients receiving cisplatin [62]; in this study, 88% of thromboembolic events occurred within the first 100 days of treatment. A meta-analysis of 8216 patients comparing cisplatin against non-cisplatin regimens in solid tumor patients similarly reported a 1.67 relative risk of VTE with cisplatin treatment [63]; subgroup analyses suggested a dose-dependent effect, with the highest doses of cisplatin demonstrating the highest thrombotic risk. Other trials of cisplatin-based regimens have reported a thrombotic incidence ranging from 8 to 18% [14, 15]. The mechanism of cisplatin-induced thrombosis is thought to be related to direct endothelial damage and augmented procoagulant effects, including increased tissue factor (TF) activity and vWF levels [15].

6.4.2 Fluorouracil

An association of fluorouracil with thrombosis has been reported in some, but not all, studies. A Surveillance, Epidemiology, and End Results (SEER) database analysis identified fluorouracil as a risk factor for VTE among 11,086 patients with metastatic colorectal cancer [64]. A single-institution study reported a VTE rate of 15% in patients receiving fluorouracil, which occurred in increased preponderance

among those with colorectal cancer [65]. A phase I study of fluorouracil in combination with granulocyte colony stimulating factor (G-CSF) in metastatic gastrointestinal cancer found a VTE incidence of up to 29% [14, 15, 66]. In other randomized controlled trials, however, VTE rates with fluorouracil have been reported to be low, in the range of 1% [67].

An acquired protein C deficiency has been reported to occur in breast cancer patients treated with fluorouracil in combination with cyclophosphamide and methotrexate [68]. Changes in levels fibrinopeptide A and thrombin have also been observed with fluorouracil and other cytotoxic chemotherapy drugs [69]. Interestingly, fluorouracil cardiotoxicity, which occurs with an incidence ranging from 4 to 19%, may underlie some instances of thrombosis via direct myocardial toxicity, arterial vasoconstriction, endothelial damage, and changes in coagulation molecules [15, 70].

Approach to treatment: Despite the reported risks of VTE with cisplatin and possibly fluorouracil, current guidelines do not recommend the use of prophylactic anticoagulation on the basis of either of these cytotoxic chemotherapy drugs alone. Patients who develop VTE on these or other cytotoxic chemotherapies should be treated with therapeutic anticoagulation according to standard guidelines.

6.5 L-Asparaginase

In 1980, a case report documented 4 incidences of CNS thrombosis and hemorrhage in children with acute lymphoblastic leukemia (ALL) on L-asparaginase therapy [71]. Subsequent studies in ALL patients treated with L-asparaginase have reported thrombosis rates of up to 5% in children and 34% in adults [72]. The classic thrombotic manifestation associated with L-asparaginase is CNS thrombosis, particularly intradural sinus thrombosis, although upper extremity DVT (in association with catheters), lower extremity DVT, PE, portal vein thrombosis, and stroke have also been observed [73–75].

Age is an independent risk factor for thrombosis due to L-asparaginase, with the incidence of thrombosis in patients older than 30 climbing to 42% in single-institution series [72]. Other risk factors include high-risk ALL, male gender, and a decreased response rate during induction treatment [76–78]. In a meta-analysis of 17 trials of pediatric ALL patients, a lower daily dose and higher number of total days of L-asparaginase treatment were both associated with increased thrombosis, the former possibly a function of the intensity of other cytotoxic chemotherapies used [79].

L-asparaginase is believed to induce thrombosis through perturbations in normal hemostasis, as depletion of L-asparagine decreases hepatic production of both natural procoagulants and anticoagulants, including protein C, protein S, antithrombin, and fibrinogen [15, 80]. Among these factors, acquired antithrombin deficiency may be the most strongly correlated with thrombosis [81]. Plasma or antithrombin replacement raises antithrombin levels in patients with ALL who are

treated with L-asparaginase and may decrease the risk of thrombosis as well, but this remains investigational [76, 81–84].

Approach to treatment: Patients with ALL who receive L-asparaginase may be considered for prophylactic anticoagulation with LMWH. In such patients, routine measurements of antithrombin, and the use of plasma or antithrombin replacement, are performed at some, but not all, centers. ALL patients who develop thrombosis on L-asparaginase should be given therapeutic anticoagulation for the duration of the time that they receive L-asparaginase and may be candidates for antithrombin replacement.

6.6 Targeted Therapies

6.6.1 VEGF Inhibitors

Monoclonal antibodies directed against VEGF have been reported to be associated with venous and arterial thrombosis, but also hemorrhage. However, the specific associations have varied according to different studies. In a phase II trial comparing 5-FU and leucovorin with and without bevacizumab for treatment of metastatic colorectal cancer, venous or arterial thrombosis was observed in 19% of patients in the bevacizumab arm versus 9% of the non-bevacizumab arm [85]. A meta-analysis of 7956 patients on 15 randomized controlled trials of bevacizumab in advanced solid tumors demonstrated a relative risk of 1.33 for VTE in patients taking bevacizumab versus control [86]; the elevated risk was similar for patients on low- and high-dose bevacizumab. Another meta-analysis in colorectal cancer, which studied 13,185 patients on 22 randomized controlled trials, also reported significantly increased risks of venous and arterial thrombotic events (relative risks of 1.244 and 1.627, respectively) [87].

By contrast, a separate meta-analysis of 1700 patients with metastatic colorectal, breast, or non-small cell lung cancer from five randomized controlled trials found no difference in VTE rates for patients irrespective of bevacizumab use, although bevacizumab-treated patients had a higher rate of arterial thrombosis [88]. A CALGB randomized controlled trial of patients with metastatic castration-resistant prostate cancer treated with docetaxel and prednisone with or without bevacizumab also found an increase in arterial but not venous thrombosis in the bevacizumab arm [89]. Another large, randomized controlled trial of metastatic colorectal cancer patients treated with irinotecan, fluorouracil, and leucovorin with or without bevacizumab found no significant difference in VTE in the two arms [14]. A systematic review examining the thrombotic risk associated with epidermal growth factor (EGFR) inhibitors reported no increased risk in those receiving bevacizumab [90]. Curiously, a SEER database study of 11,086 patients with metastatic colorectal cancer actually found a lower risk of VTE in patients who received bevacizumab [64].

Taken together, the impression from these studies is that the risk of arterial events with bevacizumab is supported, while the risk of VTE is uncertain. Aspirin does not appear to adequately prevent arterial thrombosis in bevacizumab-treated patients and may lead to increased hemorrhage [88].

A study of colorectal cancer patients identified obesity, prior VTE events, ESA use, cardiac disease, and use of exogenous hormones as predictors of thrombosis in bevacizumab-treated patients [91]. Another study of ovarian cancer patients treated with bevacizumab identified a high body mass index and elevated pretreatment D-dimer level as thrombotic risk factors [92]. The mechanisms by which bevacizumab might lead to increased arterial and/or venous thrombosis are uncertain. Hypertension induced by bevacizumab may provide the basis for some arterial events [93]. Changes in VEGF may alter expression of proinflammatory genes, with consequent effects on the potential for thrombus formation on endothelial cells [94]. VEGF effects may also lead to changes in nitric oxide and prostacyclin production, which can alter platelet function [93].

Tyrosine kinase inhibitors (TKI) with VEGF inhibition have also been implicated in thrombosis. A phase I trial of semaxanib demonstrated 8 out of 19 patients had VTE, which ultimately prevented the drug from getting to market [12]. Newer generation TKIs such as sorafenib, sunitinib, pazopanib, and vandetanib have not been found to increase thrombosis in meta-analyses [15, 95].

6.6.2 EGFR Inhibitors

EGFR inhibitors like cetuximab and panitumumab have been tied to a significant increase in VTE. A systematic review of phase II and III randomized control trials comparing standard regimens with and without an EGFR inhibitor found a RR of 1.5 for VTE and a RR of 1.6 for PE [90].

Approach to treatment: While a risk of arterial thrombosis with VEGF inhibitor treatment is well defined, a risk of VTE has been debated in the literature. Thromboprophylaxis with aspirin or LMWH is not indicated on the basis of VEGF or EGFR inhibitor use. In patients on a VEGF or EGFR inhibitor who develop a thrombotic event, the decision to continue or discontinue the inhibitor must be individualized.

6.7 Other Cancer Therapies

6.7.1 Supportive Therapies

ESA use confers an increase in thrombosis risk in cancer patients. A Cochrane review of 57 trials found relative risks of 1.5–1.67 for VTE in cancer patients receiving ESAs [96, 97]. A prospective study evaluating thrombotic risk factors in cancer patients also reported EPO as a significant risk with an odds ratio of 1.83

[98]. An increase in incidence of VTE from 3 to 23% with ESA use was reported in a trial of vaginal or cervical cancer patients undergoing chemoradiation [14]. By contrast, ESAs do not appear to increase the risk of DVT in myelodysplastic syndrome [99].

The use of G-CSF in patients with gastrointestinal cancer, lung cancer, and lymphoma was reported to have an odds ratio of 2.09 for VTE in a prospective trial [98]. Healthy patients receiving G-CSF for stem cell donation have increased procoagulant factors including von Willebrand factor, thrombomodulin, thrombin–antithrombin complexes, D-dimer, and prothrombin fragment, which may affect some of this risk [15].

Glucocorticoids are observed to increase clotting factors VII, VIII, XI, and fibrinogen in healthy controls [15]. Cancer patients receiving high-dose steroids for nausea have been an odds ratio of 3.5 for VTE [14]. Similarly, a large case-control study involving nearly 39,000 patients on steroids for a variety of indications found VTE was 2.3 times more likely in the group receiving steroids compared to controls [100].

6.7.2 Radiation Therapy

Although radiation is known to induce inflammation, endothelial activation, and cell death, it has not been definitively associated with thrombosis. A retrospective analysis of 9284 French cancer patients with prior VTE found higher rates of PE recurrence while on anticoagulation for patients receiving radiation compared to those not [101]. However, the subgroup analysis examining rates of DVT found no significant difference and overall recurrent VTE rates were not significantly different. Likewise, radiation was not identified as a significant thrombotic risk factor in a prospective study [98].

References

1. Sorensen HT et al (2000) Prognosis of cancers associated with venous thromboembolism. N Engl J Med 343(25):1846–1850
2. Khorana AA et al (2013) Incidence and predictors of venous thromboembolism (VTE) among ambulatory high-risk cancer patients undergoing chemotherapy in the United States. Cancer 119(3):648–655
3. Navi BB et al (2017) Risk of arterial thromboembolism in patients with cancer. J Am Coll Cardiol 70(8):926–938
4. Timp JF et al (2013) Epidemiology of cancer-associated venous thrombosis. Blood 122 (10):1712–1723
5. Heit JA et al (2000) Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med 160(6):809–815
6. Davies C et al (2011) Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 378 (9793):771–784

7. Lyman GH et al (2007) American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. J Clin Oncol 25(34):5490–5505
8. Nevasaari K, Heikkinen M, Taskinen PJ (1978) Tamoxifen and thrombosis. Lancet 2 (8096):946–947
9. Conard J et al (1980) L-asparaginase, antithrombin III, and thrombosis. Lancet 1(8177):1091
10. Deitcher SR, Gomes MP (2004) The risk of venous thromboembolic disease associated with adjuvant hormone therapy for breast carcinoma: a systematic review. Cancer 101(3):439–449
11. Fisher B et al (1999) Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. Lancet 353 (9169):1993–2000
12. Zangari M et al (2009) Thrombotic events in patients with cancer receiving antiangiogenesis agents. J Clin Oncol 27(29):4865–4873
13. Khorana AA et al (2007) Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. Cancer 110(10):2339–2346
14. Haddad TC, Greeno EW (2006) Chemotherapy-induced thrombosis. Thromb Res 118 (5):555–568
15. Oppelt P, Betbadal A, Nayak L (2015) Approach to chemotherapy-associated thrombosis. Vasc Med 20(2):153–161
16. Cuzick J et al (2002) First results from the International Breast Cancer Intervention Study (IBIS-I): a randomised prevention trial. Lancet 360(9336):817–824
17. Fisher B et al (1998) Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 90(18):1371–1388
18. Fisher B et al (1996) Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. J Natl Cancer Inst 88(21):1529–1542
19. Fisher B et al (1997) Tamoxifen and chemotherapy for lymph node-negative, estrogen receptor-positive breast cancer. J Natl Cancer Inst 89(22):1673–1682
20. Hernandez RK et al (2009) Tamoxifen treatment and risk of deep venous thrombosis and pulmonary embolism: a Danish population-based cohort study. Cancer 115(19):4442–4449
21. Abramson N et al (2006) Effect of Factor V Leiden and prothrombin G20210→A mutations on thromboembolic risk in the national surgical adjuvant breast and bowel project breast cancer prevention trial. J Natl Cancer Inst 98(13):904–910
22. Decensi A et al (2005) Effect of tamoxifen on venous thromboembolic events in a breast cancer prevention trial. Circulation 111(5):650–656
23. Garber JE et al (2010) Factor V Leiden mutation and thromboembolism risk in women receiving adjuvant tamoxifen for breast cancer. J Natl Cancer Inst 102(13):942–949
24. Duggan C et al (2003) Inherited and acquired risk factors for venous thromboembolic disease among women taking tamoxifen to prevent breast cancer. J Clin Oncol 21(19):3588–3593
25. Eroglu A, Akar N (2011) Factor V Leiden, prothrombin G20210A and methylenetetrahydrofolate reductase (MTHFR) C677T polymorphisms and the risk of tamoxifen-associated thromboembolism in breast cancer patients. Thromb Res 127(4):384–385
26. Hackshaw A et al (2011) Long-term benefits of 5 years of tamoxifen: 10-year follow-up of a large randomized trial in women at least 50 years of age with early breast cancer. J Clin Oncol 29(13):1657–1663
27. Ettinger B et al (1999) Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. Jama 282(7):637–645

28. Adomaityte J, Farooq M, Qayyum R (2008) Effect of raloxifene therapy on venous thromboembolism in postmenopausal women. A meta-analysis. Thromb Haemost 99 (2):338–342
29. Vogel VG et al (2006) Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA 295(23):2727–2741
30. Goss PE et al (2005) Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. J Natl Cancer Inst 97(17):1262–1271
31. Baum M et al (2002) Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet 359(9324):2131–2139
32. Rajkumar SV et al (2002) Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. J Clin Oncol 20(21):4319–4323
33. Zangari M et al (2001) Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy. Blood 98(5):1614–1615
34. Palumbo A et al (2008) Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia 22(2):414–423
35. Dimopoulos MA et al (2014) Expert panel consensus statement on the optimal use of pomalidomide in relapsed and refractory multiple myeloma. Leukemia 28(8):1573–1585
36. Zangari M et al (2003) The blood coagulation mechanism in multiple myeloma. Semin Thromb Hemost 29(3):275–282
37. Knight R, DeLap RJ, Zeldis JB (2006) Lenalidomide and venous thrombosis in multiple myeloma. N Engl J Med 354(19):2079–2080
38. Rajkumar SV et al (2008) Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma. J Clin Oncol 26(13):2171–2177
39. Zangari M et al (2011) Low venous thromboembolic risk with bortezomib in multiple myeloma and potential protective effect with thalidomide/lenalidomide-based therapy: review of data from phase 3 trials and studies of novel combination regimens. Clin Lymphoma Myeloma Leuk 11(2):228–236
40. Leonard JP et al (2015) Randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma: CALGB 50401 (Alliance). J Clin Oncol 33(31):3635–3640
41. Yamshon S et al (2017) Venous thromboembolism in patients with B-cell non-Hodgkin lymphoma (NHL) treated with lenalidomide. Blood 130:122
42. Brandenburg NA et al (2008) Venous thromboembolism in patients with myelodysplastic syndrome treated with lenalidomide: incidence and risk factors. J Clin Oncol 15_Suppl:7084
43. Kaushal V et al (2004) Thalidomide protects endothelial cells from doxorubicin-induced apoptosis but alters cell morphology. J Thromb Haemost 2(2):327–334
44. Abdullah WZ et al (2013) Increased PAC-1 expression among patients with multiple myeloma on concurrent thalidomide and warfarin. Blood Coagul Fibrinolysis 24(8):893–895
45. Rodeghiero F, Elice F (2003) Thalidomide and thrombosis. Pathophysiol Haemost Thromb 33(Suppl 1):15–18
46. Corso A et al (2004) Modification of thrombomodulin plasma levels in refractory myeloma patients during treatment with thalidomide and dexamethasone. Ann Hematol 83(9):588–591
47. Zappasodi P et al (2006) Thrombomodulin levels are not modified during thalidomide treatment. Eur J Haematol 77(5):453–454
48. Pal R et al (2010) Immunomodulatory derivatives induce PU.1 down-regulation, myeloid maturation arrest, and neutropenia. Blood 115(3):605–614
49. Palumbo A, Palladino C (2012) Venous and arterial thrombotic risks with thalidomide: evidence and practical guidance. Ther Adv Drug Saf 3(5):255–266

50. Zangari M et al (2002) Activated protein C resistance in the absence of factor V Leiden mutation is a common finding in multiple myeloma and is associated with an increased risk of thrombotic complications. Blood Coagul Fibrinolysis 13(3):187–192
51. Talamo GP et al (2009) Hypercoagulable states in patients with multiple myeloma can affect the thalidomide-associated venous thromboembolism. Blood Coagul Fibrinolysis 20(5):337–339
52. Bagratuni T et al (2013) Clinical and genetic factors associated with venous thromboembolism in myeloma patients treated with lenalidomide-based regimens. Am J Hematol 88 (9):765–770
53. Johnson DC et al (2008) Genetic associations with thalidomide mediated venous thrombotic events in myeloma identified using targeted genotyping. Blood 112(13):4924–4934
54. Zangari M et al (2008) Hemostatic effects of bortezomib treatment in patients with relapsed or refractory multiple myeloma. Haematologica 93(6):953–954
55. Larocca A et al (2012) Aspirin or enoxaparin thromboprophylaxis for patients with newly diagnosed multiple myeloma treated with lenalidomide. Blood 119(4):933–939; quiz 1093
56. Palumbo A et al (2011) Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with thalidomide: a phase III, open-label, randomized trial. J Clin Oncol 29(8):986–993
57. Lyman GH et al (2013) Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 31(17):2189–2204
58. Kristinsson SY (2010) Thrombosis in multiple myeloma. Hematol Am Soc Hematol Educ Program 2010:437–444
59. Greeno EW, Bach RR, Moldow CF (1996) Apoptosis is associated with increased cell surface tissue factor procoagulant activity. Lab Invest 75(2):281–289
60. Wang J et al (2001) Thrombogenic role of cells undergoing apoptosis. Br J Haematol 115 (2):382–391
61. Rogers JS 2nd et al (1988) Chemotherapy for breast cancer decreases plasma protein C and protein S. J Clin Oncol 6(2):276–281
62. Zahir MN et al (2017) Incidence of Venous Thromboembolism in cancer patients treated with Cisplatin based chemotherapy—a cohort study. BMC Cancer 17(1):57
63. Seng S et al (2012) Risk of venous thromboembolism in patients with cancer treated with Cisplatin: a systematic review and meta-analysis. J Clin Oncol 30(35):4416–4426
64. Pulluri B et al (2016) Risk factors for venous thromboembolism in metastatic colon cancer patients in the contemporary treatment era: a SEER-Medicare data analysis. Blood 128:2598
65. Otten HM et al (2004) Symptomatic venous thromboembolism in cancer patients treated with chemotherapy: an underestimated phenomenon. Arch Intern Med 164(2):190–194
66. Grem JL et al (1994) Phase I and pharmacokinetic study of recombinant human granulocyte-macrophage colony-stimulating factor given in combination with fluorouracil plus calcium leucovorin in metastatic gastrointestinal adenocarcinoma. J Clin Oncol 12 (3):560–568
67. Tournigand C et al (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 22(2):229–237
68. Feffer SE, Carmosino LS, Fox RL (1989) Acquired protein C deficiency in patients with breast cancer receiving cyclophosphamide, methotrexate, and 5-fluorouracil. Cancer 63 (7):1303–1307
69. Edwards RL et al (1990) Heparin abolishes the chemotherapy-induced increase in plasma fibrinopeptide A levels. Am J Med 89(1):25–28
70. Polk A et al (2014) A systematic review of the pathophysiology of 5-fluorouracil-induced cardiotoxicity. BMC Pharmacol Toxicol 15:47
71. Priest JR et al (1980) Thrombotic and hemorrhagic strokes complicating early therapy for childhood acute lymphoblastic leukemia. Cancer 46(7):1548–1554

72. Grace RF et al (2011) The frequency and management of asparaginase-related thrombosis in paediatric and adult patients with acute lymphoblastic leukaemia treated on Dana-Farber Cancer Institute consortium protocols. Br J Haematol 152(4):452–459
73. Gugliotta L et al (1992) Incidence of thrombotic complications in adult patients with acute lymphoblastic leukaemia receiving L-asparaginase during induction therapy: a retrospective study. The GIMEMA Group. Eur J Haematol 49(2):63–66
74. Lederman GS (1982) Stroke due to treatment with L-asparaginase in an adult. N Engl J Med 307(26):1643
75. Mitchell LG et al (2003) A prospective cohort study determining the prevalence of thrombotic events in children with acute lymphoblastic leukemia and a central venous line who are treated with L-asparaginase: results of the Prophylactic Antithrombin Replacement in Kids with Acute Lymphoblastic Leukemia Treated with Asparaginase (PARKAA) Study. Cancer 97(2):508–516
76. Abbott LS et al (2009) The impact of prophylactic fresh-frozen plasma and cryoprecipitate on the incidence of central nervous system thrombosis and hemorrhage in children with acute lymphoblastic leukemia receiving asparaginase. Blood 114(25):5146–5151
77. Lauw MN et al (2013) Venous thromboembolism in adults treated for acute lymphoblastic leukaemia: effect of fresh frozen plasma supplementation. Thromb Haemost 109(4):633–642
78. Santoro N et al (2013) Screening for coagulopathy and identification of children with acute lymphoblastic leukemia at a higher risk of symptomatic venous thrombosis: an AIEOP experience. J Pediatr Hematol Oncol 35(5):348–355
79. Caruso V et al (2006) Thrombotic complications in childhood acute lymphoblastic leukemia: a meta-analysis of 17 prospective studies comprising 1752 pediatric patients. Blood 108 (7):2216–2222
80. Goyal G, Bhatt VR (2015) L-asparaginase and venous thromboembolism in acute lymphocytic leukemia. Future Oncol 11(17):2459–2470
81. Couturier MA et al (2015) Cerebral venous thrombosis in adult patients with acute lymphoblastic leukemia or lymphoblastic lymphoma during induction chemotherapy with L-asparaginase: The GRAALL experience. Am J Hematol 90(11):986–991
82. Farrell K et al (2016) An antithrombin replacement strategy during asparaginase therapy for acute lymphoblastic leukemia is associated with a reduction in thrombotic events. Leuk Lymphoma 57(11):2568–2574
83. Hunault-Berger M et al (2008) Changes in antithrombin and fibrinogen levels during induction chemotherapy with L-asparaginase in adult patients with acute lymphoblastic leukemia or lymphoblastic lymphoma. Use of supportive coagulation therapy and clinical outcome: the CAPELAL study. Haematologica 93(10):1488–1494
84. Meister B et al (2008) Comparison of low-molecular-weight heparin and antithrombin versus antithrombin alone for the prevention of symptomatic venous thromboembolism in children with acute lymphoblastic leukemia. Pediatr Blood Cancer 50(2):298–303
85. Kabbinavar F et al (2003) Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol 21(1):60–65
86. Nalluri SR et al (2008) Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. JAMA 300(19):2277–2285
87. Alahmari AK et al (2016) Thromboembolic events associated with bevacizumab plus chemotherapy for patients with colorectal cancer: a meta-analysis of randomized controlled trials. Am Health Drug Benefits 9(4):221–232
88. Scappaticci FA et al (2007) Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. J Natl Cancer Inst 99(16):1232–1239
89. Patel JN et al (2015) Bevacizumab and the risk of arterial and venous thromboembolism in patients with metastatic, castration-resistant prostate cancer treated on Cancer and Leukemia Group B (CALGB) 90401 (Alliance). Cancer 121(7):1025–1031

90. Miroddi M et al (2016) Systematic review and meta-analysis of the risk of severe and life-threatening thromboembolism in cancer patients receiving anti-EGFR monoclonal antibodies (cetuximab or panitumumab). Int J Cancer 139(10):2370–2380
91. Roddy JV et al (2010) Thromboembolic events in patients with colorectal cancer receiving the combination of bevacizumab-based chemotherapy and erythropoietin stimulating agents. Am J Clin Oncol 33(1):36–42
92. Kuk A et al (2017) Retrospective evaluation of thromboembolism risk in ovarian cancer patients treated with bevacizumab. Target Oncol 12(4):495–503
93. DeLoughery TG, Beer TM (2015) Bevicizumab and thrombosis: some answers but questions remain. Cancer 121(7):975–977
94. Ferroni P et al (2010) Thromboembolic events in patients treated with anti-angiogenic drugs. Curr Vasc Pharmacol 8(1):102–113
95. Qi WX et al (2013) Risk of venous thromboembolic events associated with VEGFR-TKIs: a systematic review and meta-analysis. Int J Cancer 132(12):2967–2974
96. Tonia T et al (2012) Erythropoietin or darbepoetin for patients with cancer. Cochrane Database Syst Rev 12:Cd003407
97. Bohlius J et al (2006) Erythropoietin or darbepoetin for patients with cancer. Cochrane Database Syst Rev (3):CD003407
98. Khorana AA et al (2005) Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. Cancer 104(12):2822–2829
99. Smith SW et al (2012) Erythropoiesis-stimulating agents are not associated with increased risk of thrombosis in patients with myelodysplastic syndromes. Haematologica 97(1):15–20
100. Johannesdottir SA et al (2013) Use of glucocorticoids and risk of venous thromboembolism: a nationwide population-based case-control study. JAMA Intern Med 173(9):743–752
101. Guy JB et al (2017) Venous thromboembolism in radiation therapy cancer patients: findings from the RIETE registry. Crit Rev Oncol Hematol 113:83–89

7 Treatment of Venous Thromboembolism in Cancer. Historical Perspective and Evolving Role of the Direct Oral Anticoagulants

Marc Carrier, Gerald Soff and Grégoire Le Gal

Contents

M. Carrier (✉) · G. Le Gal
Department of Medicine, Ottawa Hospital Research Institute at the University of Ottawa, Ontario, Canada
e-mail: mcarrier@toh.ca

G. Soff
Memorial Sloan Kettering Cancer Center, New York, NY, USA

M. Carrier
Ottawa Hospital, General Campus, 501 Smyth Road, Box 201A, Ottawa, ON K1H 8L6, Canada

G. Soff (ed.), *Thrombosis and Hemostasis in Cancer*, Cancer Treatment and Research 179, https://doi.org/10.1007/978-3-030-20315-3_7

7.1 History of Cancer-Associated Thrombosis

The association of venous thromboembolism (VTE) with cancer has been recognized for well over 100 years. As early as 1823, Jean-Baptiste Bouillaud published a description of cancer-associated thrombosis (CAT) [1–3]. Armand Trousseau is most widely credited with recognizing the association between VTE and cancer, publishing his treatise in 1865 [4–6]. Illtyd James and Matheson published the first description of VTE as the first sign of occult cancer in 1935 [7]. These and numerous subsequent articles led to the appreciation that VTE is common and associated with increased morbidity and mortality among cancer patients [8–10]. The focus of this chapter will be to provide a historical perspective and summary of the evidence of the different anticoagulants for the management of cancer-associated thrombosis (CAT).

7.2 Historical Perspective on the Management of Venous Thromboembolism

Heparin was discovered in 1916 and has been used in humans as early as 1935 [11, 12]. The first study of unfractionated heparin (UFH) in patients with acute VTE was published in 1938 [13]. Oral vitamin K antagonists (VKAs), such as warfarin, were introduced shortly after and allowed for chronic anticoagulation treatment [14, 15]. Barritt and Jordan published a randomized trial of patients with pulmonary embolism in 1960, demonstrating a dramatic difference in survival with chronic anticoagulation with a VKA, thus establishing the standard of care of acute treatment with heparin, followed by chronic anticoagulation with a VKA [16].

The development of low-molecular-weight-heparin (LMWH) allowed for outpatient management of VTE. LMWH was introduced in Europe in the early 1980s and entered widespread use within 10 years [17, 18]. Many clinical trials and meta-analyses have shown that subcutaneous injections of a LMWH are comparable to continuous infusions of UFH for initial therapy; however, oral VKA remained the cornerstone of anticoagulation for long-term treatment or secondary prevention [19].

However, VKA use is known to be particularly challenging in cancer patients. Prandoni and colleagues published that treatment of VTE in cancer patients with a VKA was associated with significantly higher rates of recurrent thrombosis (Hazard Ratio 3.2) and significantly higher rates of major bleeding (Hazard ratio 2.2), compared with non-cancer patients with VTE [20]. Cancer patients have inconsistent diet, nausea/vomiting, and diarrhea from cancer-directed therapy, and frequent drug–drug interactions that can lead to unpredictable anticoagulant responses to VKA. It is no surprise that VKA use is associated with high rates of failure and bleeding.

Given the aggressive natural history of VTE in cancer patients, their comorbid conditions, numerous potential drug interactions, and their heightened risk of bleeding, it is important to evaluate the efficacy and safety of anticoagulation specifically in the cancer population.

7.3 Treatment of Cancer-Associated Thrombosis

The management of cancer-associated thrombosis is complex. In addition to higher rates of recurrence and bleeding, thrombotic complications can delay or interfere with first-line anticancer therapy, precipitate or prolong hospitalization, and consume healthcare resources. Therefore, effective and appropriate treatment of VTE is an important strategy for minimizing morbidity and mortality, and potentially increases patient quality of life and reduces healthcare costs.

7.3.1 Initial Treatment of Cancer-Associated Thrombosis (First 5–7 Days)

Traditionally, initial treatment for an acute episode of VTE is the same for patients with or without cancer. No study has demonstrated significant differences in safety or efficacy with acute treatment of CAT with UFH, LMWH, or fondaparinux. The major advantage of LMWH over UFH is its availability for outpatient management.

Table 7.1 Randomized controlled trials for long-term treatment of VTE associated with cancer

Trial	*N*	Intervention	Duration	Major bleeding (%)	Recurrent VTE (%)	Death (%)
CANTHANOX [23]	67	Enoxaparin 1.5 mg/Kg/OD	3 months	7	3	22.7
	71	VKA		16	4.2	11.3
CLOT [24]	336	Dalteparin (200 IU/Kg/OD) X 1 month then 150 IU/Kg X 5 months	6 months	4	9	39
	336	VKA		6	17	41
ONCENOX[a] [25]	29	Enoxaparin 1 mg/Kg/OD	3 months	6.5	6.9	6.5
	32	Enoxaparin 1.5 mg/Kg OD		11.1	6.3	19.4
	30	VKA		2.9	10	8.8
LITE [26]	100	Tinzaparin (175 IU/Kg/OD)	3 months	7	6	19
	100	VKA		7	10	20
CATCH [27]	449	Tinzaparin (175 IU/Kg/OD)	6 months	2.7	7.2	33
	451	VKA		2.4	10.5	31

[a]All groups started with enoxaparin 1 mg/kg BID × 5 days

This availability makes LMWH an attractive therapeutic option for cancer patients with acute VTE because it reduces hospitalization and improves quality of life. Data indicate that VTE treated at home with LMWH in cancer patients is safe and feasible in most of the cases [21]. Fondaparinux has a long half-life and renal clearance. Therefore, LMWH was recommended for the initial treatment of cancer-associated thrombosis [22].

7.3.2 Chronic Treatment of Cancer-Associated Thrombosis (Initial 3–6 Months, and Beyond)

Oral VKA anticoagulant therapy with adjustment to maintain a target international normalized ratio (INR) of 2.0–3.0 was the mainstay of long-term anticoagulation for CAT over many decades, but as noted, was particularly challenging. This led to a series of clinical trials comparing LMWH to VKA for chronic treatment of CAT. A total of five trials have compared LMWH with VKA for the treatment of acute CAT (Table 7.1).

The first report comparing LMWH (enoxaparin) and VKA was the CANTHANOX study in 2002 [23]. A non-significant trend toward lower recurrent thrombosis and less major bleeding was encouraging. A total of 21% of the patients assigned to VKA experienced major bleeding or recurrent VTE, as compared with 10.5% of patients assigned to enoxaparin ($P = 0.09$) [23]. Also of note, the death rate was actually twice as high in the LMWH group. However, the study was limited by small numbers and the use of a combined endpoint of recurrent VTE and major bleeding. Therefore, no conclusions could be drawn [23].

The landmark CLOT trial, published in 2003, compared dalteparin to VKA for chronic anticoagulation, and was the first definitive study to demonstrate superior efficacy of LWMH over VKA. There was an approximately 50% relative risk reduction in recurrent thrombosis in six months [24]. In this study, the LMWH group received dalteparin at a therapeutic dose for the first month followed by 75–80% of the full dose for the next five months. There were no significant differences in the rates of major bleeding episodes or death between the two groups.

More recently, the CATCH trial which randomized patients with CAT to therapeutic doses of tinzaparin (i.e. no dose reduction) or VKA was reported [27]. Although the trial reported a 35% reduction in the cumulative risk of recurrent CAT for patients receiving LMWH, this was not statistically significant ($P = 0.07$). Similarly, there were no differences in the rates of major bleeding episodes or death between the two groups, but the patients receiving tinzaparin had a lower risk of clinically relevant non-major bleeding. A systematic review and meta-analysis combining the results of all the randomized controlled trials comparing LMWH to VKA for the management of CAT supports the conclusion that LMWH is associated with a significant reduction in the risk of recurrent VTE (RR: 0.56; 95% CI: 0.43–0.74) without a significant difference in the risk of major bleeding episodes (RR: 1.07; 95% CI: 0.66–1.73) [28, 29]. Therefore, the consensus has been that

LMWH has a favorable benefit-risk profile for the management of cancer-associated thrombosis compared with VKA and have been recommended by international clinical practice guidelines [22, 30].

7.3.2.1 Direct Oral Anticoagulants

Over the last decade, there has been an exciting introduction into practice of the direct oral anticoagulants (DOACs). The DOACs include the direct thrombin inhibitor (dabigatran) and the direct Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban, and betrixaban). In a growing range of indications, DOACs offer an attractive alternative for the treatment of thrombosis as well as prophylaxis. Unlike LMWH, they are administered orally and have less drug–drug interactions and dietary limitations than VKA.

Randomized controlled trials have shown that DOACs are comparable to VKA for the treatment of VTE in the general population. Three systematic reviews and meta-analyses assessing the efficacy and safety of DOACs for the treatment VTE specifically in cancer subgroups have been published [28, 31, 32]. Overall, 1132 patients with CAT were included in the analyses and showed that using a DOAC was associated with trends toward lower risk of recurrent VTE (RR: 0.66; 95% CI: 0.39–1.11) and major bleeding episodes (RR: 0.78; 95% CI: 0.42–1.44) compared to VKA. The eligibility criteria for the parent studies in those meta-analyses, however, tended to exclude the most complicated cancer patients. The cancer patients receiving DOACs included in these meta-analyses had a lower annualized risk of recurrent VTE and major bleeding, suggesting that lower-risk cancer patients were included, compared to the patients included in the CAT trials (e.g., CLOT and CATCH trials) [28].

A network meta-analysis based on indirect comparisons also suggested that DOACs may also have similar effectiveness and safety to LMWHs for the management of cancer-associated thrombosis [33]. Although the efficacy and safety of DOACs in this specific patient population seemed to be comparable to those of VKA or LMWH, the quality of evidence was low considering that the trials were underpowered to show non-inferiority or superiority of DOACs to VKA in cancer patients. Therefore, clinical guidelines continued to recommend LMWHs over DOACs as the preferred initial treatment of CAT due to the lack of high-quality data from dedicated trials as recently as 2016 [34].

Nonetheless, the use of DOACs for the treatment of cancer-associated thrombosis has been growing. Due to the pain and cost from chronic LMWH use, only approximately 50% of patients adhere to long-term treatment with LMWH despite strong recommendations from clinical practice guidelines [35]. Patients and treating physicians were anxious for a less burdensome alternative. Further, the FDA approved rivaroxaban in 2012 for treatment of DVT and PE, and did not explicitly address thrombosis in the setting of cancer. Therefore, starting late 2012 when rivaroxaban was approved for VTE treatment, there has been increasing the use and multiple observational cohort studies published supporting safe and effective use of DOACs in CAT [36–40]. Fairly abundant real-world data preceded the first

randomized clinical trials, comparing a DOAC with LMWH, which were published in late 2017 and 2018 [41, 42].

A recently published systematic review summarized the incidence of recurrent VTE and major bleeding episodes in over 5000 patients with CAT [43] treated with DOACs. Overall, the on-treatment duration of DOAC use was usually longer than that of LMWH which may reflect unstated patient preferences for oral agents or cost barriers. A majority of the included studies reported lower rates of recurrent VTE for patients on DOACs as compared to those on LMWHs [43]. Major bleeding outcomes were heterogeneous across these studies.

At one of our institutions (GAS at Memorial Sloan-Kettering Cancer Center), we established a Clinical Pathway in 2013, to guide the use of rivaroxaban for the treatment of CAT [36–40]. The key was patient selection. An oral direct anticoagulant would entail biologically active concentrations within the gastrointestinal tract lumen, with a high risk of GI bleeding in the presence of GI lesions. Similarly, rivaroxaban and other DOACs are renally cleared and would be concentrated in the genito-urinary (GU) tract. LMWH is also cleared by the kidney but would not exert an anticoagulant effect in the absence of antithrombin III. Therefore, our clinical pathway specified that patients with GI or GU lesions were to be treated with a LMWH, while others without those contraindications can be treated with rivaroxaban [36–40]. With the MSKCC Clinical Pathway, six-month rates of recurrent thrombosis (4.4%, 95% CI = 1.4–7.4%) and major bleeding (2.2%, 95% CI = 0−4.2%) were lower than historical controls treated with LMWH [36–40].

Recently, two randomized controlled trials (HOKUSAI-Cancer and SELECT-D) comparing DOACs to LMWH for the treatment of cancer-associated thrombosis have been published (see Table 7.2) [41, 42]. The HOKUSAI-Cancer was an open-label, non-inferiority trial that randomized 1050 patients with cancer and acute symptomatic or incidental VTE to LMWH for at least five days followed by oral edoxaban 60 mg once daily or dalteparin [41]. Treatment was given for at least six and up to 12 months. The primary outcome was a composite of recurrent VTE or major bleeding during 12 months after randomization and occurred in 12.8 and 13.5% of patients receiving edoxaban and dalteparin (HR, 0.97; 95% CI, 0.70–1.36; P = 0.006 for non-inferiority), respectively. There was a non-significant trend to a lower rate of recurrent VTE with edoxaban (HR 0.71, 95% CI 0.48–1.06). However, the rate of major bleeding episodes was higher in patients receiving the edoxaban (HR 1.77, 95% CI 1.03–3.04). The difference in major bleeding episodes between the groups was mostly related to the upper gastrointestinal bleeding event, especially in patients with gastrointestinal cancers on edoxaban.

Select-D was a prospective, randomized, open-label, multicenter pilot trial randomizing 406 cancer patients with acute CAT to dalteparin or rivaroxaban (Table 7.2) [42]. The results were similar to the HOKUSAI-Cancer study; rivaroxaban showed a trend toward a lower rate of recurrent thrombosis with rivaroxaban compared with dalteparin, (3.9% vs. 8.9%), and a trend toward higher rate of bleeding (5.4% vs. 3%), although neither trend was significant [42]. Gastrointestinal cancer patients were especially at risk for bleeding, so much so that

Table 7.2 Randomized controlled trials of DOACs for long-term treatment of cancer-associated thrombosis

Trial	N	Intervention	Duration	Major bleeding (%)	Recurrent VTE (%)	Death (%)
HOKUSAI-Cancer [41]	522	Edoxaban[a]	12 months	6.9	7.9	39.5
	524	Dalteparin (200 IU/Kg/OD) × 1 month then 150 IU/Kg × 5 months		4	11.3	36.6
Select-D [42]	203	rivaroxaban 15 mg BID × 21 days then 20 mg OD	6 months	5.4	3.9	24
	203	Dalteparin (200 IU/Kg/OD) × 1 month then 150 IU/Kg × 5 months		3	8.9	27

[a]Patient received at least five days of therapeutic LMWH

upper gastrointestinal cancer (gastric and gastro-esophageal junction tumors) patients were excluded toward the end of the study.

A meta-analysis of these two trials showed that DOACs had a lower incidence of six-month recurrent VTE when compared to LMWHs [RR: 0.65 (95% CI: 0.42–1.01)]. However, DOACs had a higher incidence of six-month major bleeding when compared to LMWHs [RR: 1.74 (95% CI: 1.05–2.88)] [43]. Similarly, clinically relevant non-major bleeding was higher [RR: 2.31 (95% CI: 0.85–6.28)] for patients with cancer-associated thrombosis receiving a DOAC. There was no difference in mortality [RR: 1.03 (95% CI: 0.85–1.26)].

7.3.2.2 Guidance on the Management of Acute Cancer-Associated Thrombosis

Several factors need to be considered to assess the risk: benefit ratio of the different anticoagulant options in the acute treatment of cancer-associated thrombosis. Clinicians need to make an individual treatment decision and tailor anticoagulant needs based on the patient's characteristics and preferences. The perceived benefits of DOACs (oral administration, lower recurrent VTE rate, and no monitoring) need to be considered against their perceived negative attributes (increased bleeding and potential drug–drug interactions) and the strength of value an individual patient gives to each feature. Drug–drug interactions of DOACs with anticancer therapy that inhibit or induce P-glycoprotein or cytochrome P450 3A4 are important to consider [44, 45]. Furthermore, there is a perception among clinicians that subcutaneous injections of LMWH might be too burdensome and unacceptable for cancer patients. Qualitative studies have shown that cancer patients view LMWH injections as inconsequential compared to other interventions encountered during their cancer journey [46, 47]. Patients consider the most important attribute of their anticoagulation regimen to be that it does not interfere with their cancer treatment. Efficacy and safety are the second and third most important attributes followed by the preference of oral instead of a parenteral route of administration [48]. Therefore, clinical decision making needs to weigh these competing factors within the context of individual patients' preferences and values.

With the evolving body of data, derived from prospective clinical trials as well as real-world cohort reports, there is a growing appreciation and acceptance of the use of DOACs in the cancer setting. A recently published Guidance Statement for the International Society of Thrombosis and Hemostasis (in which two of us have been co-authors) recommends individualized treatment regimen after shared decision making with patients [49]. The use of DOACs is suggested for cancer patients with an acute diagnosis of VTE, low risk of bleeding, and no drug–drug interactions with current systemic therapy. The guidelines specifically recommend "*use of specific DOACs for cancer patients with an acute diagnosis of VTE, low risk of bleeding and no drug–drug interactions with current systemic therapy. LMWHs are an acceptable alternative,*" and "*use of LMWHs for cancer patients with an acute diagnosis of VTE and high risk of bleeding, including: patients with luminal gastrointestinal cancers with an intact primary; cancers at risk of bleeding from genitourinary tract, bladder or nephrostomy tubes; or patients with active*

gastrointestinal mucosal abnormalities such as duodenal ulcers, gastritis, esophagitis or colitis. Specific DOACs (edoxaban and rivaroxaban) are an acceptable alternative if no drug–drug interactions exist with current systemic therapy." Edoxaban and rivaroxaban are the only DOACs with current randomized trial evidence compared with LMWH in cancer patients [49].

Similarly, the current NCCN guidelines for cancer-associated thrombosis (March 22, 2018), endorsed LMWH as first choice anticoagulation for CAT. [https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf]. However, the NCCN guidelines note that patients may refuse or be "poor candidates for LMWH injections because they are painful, inconvenient, and expensive." In those cases, a DOAC is a reasonable alternative, again with the qualifier to use a DOAC with caution in patients "with urinary or gastrointestinal tract lesions, pathology or instrumentation."

7.3.3 Extended Treatment (Beyond the Initial Six Months)

Data on the management of cancer-associated thrombosis beyond the initial six months of therapy is scarce. The length of anticoagulation for secondary prevention of recurrent VTE is usually guided by the presence of ongoing factors increasing the risk of recurrent VTE and/or cancer recurrence. Risk stratification based on the tumor type, stage of disease (e.g., metastatic) and patient co-morbidities is important and may help clinicians to stratify patients according to their underlying risk of developing recurrent cancer-associated thrombosis [50, 51]. Patients at high risk of recurrent VTE (active cancer, undergoing chemotherapy, etc.) may potentially benefit from indefinite anticoagulation. However, the length of anticoagulation is still debated, and it is unlikely that a clinical randomized controlled trial is feasible in this patient population to answer this important clinical question, due to strong held patient and physician preferences regarding anticoagulation [52].

Only two prospective cohort studies have evaluated the safety of extending anticoagulation with LMWH beyond the initial six months (up to 12 months) in patients with CAT [53]. In the DALTECAN study, a total of 334 patients with cancer-associated thrombosis were treated with dalteparin, of whom 185 (55.4%) completed six months of therapy and 109 (33%) completed 12 months. LMWH therapy beyond six months did not seem to be associated with an increased risk of major bleeding episodes or recurrent VTE compared to the initial period of therapy. Furthermore, the rates of recurrent VTE and major bleeding on anticoagulation therapy were similar. Therefore, the rate of recurrent CAT if anticoagulation is discontinued is likely to be higher than the major bleeding risk [53]. Similarly, the Ti-CAT study enrolled a total of 247 patients with cancer-associated thrombosis treated with tinzaparin and followed those over 12 months [54]. Overall, the incidence of the major bleeding episode was 4.9%. The rates of clinically relevant non-major bleeding over the first and second six-month periods were 0.9% (95% CI: 0.5–1.2%) and 0.6% (95% CI: 0.2–1.4%), respectively. Therefore, LMWH seems to be an attractive option given its strong data in the acute and extended

treatment of cancer-associated thrombosis. In general, one should treat CAT for at least six months of anticoagulation, and then reassess ongoing risks of recurrent thrombosis and bleeding. In a patient with active cancer, without a high risk of bleeding, indefinite anticoagulation may be the appropriate course.

The data supporting the use of DOACs beyond the initial six months of anticoagulation therapy is scarce. Although the HOKUSAI-Cancer trial followed patients for up to 12 months, the details on the efficacy and safety of DOACs beyond the initial six months of anticoagulation remains unknown. However, some patients might prefer to consider an alternative oral anticoagulant instead of the parenteral LMWH injections. The Guidance document from the SCC of the ISTH suggests that for patients who are currently on anticoagulation for a prior diagnosis of cancer-associated thrombosis for whom indefinite anticoagulation is being considered, a discussion about continuing on current anticoagulation versus transitioning to a different class of anticoagulants be conducted. DOACs, LMWHs, and VKAs are all acceptable options in patients who have completed six months of anticoagulation, given lack of data to support any one class of anticoagulants in this setting.

In conclusion, the management of anticoagulant therapy for a patient with CAT is complex. Clinicians need to tailor anticoagulation management based on the risk-benefit profiles on a case-by-case basis. Cancer patients are highly heterogeneous with a variety of different tumor types (with different risks of recurrent VTE and major bleeding complications), anticancer treatments (with different drug–drug interactions), co-morbidities, experiences, and preferences. The recent data on the DOACs for the management of cancer-associated thrombosis provides clinicians with new options of treatment. The emphasis needs to be on patient selection and tailored anticoagulation treatment.

References

1. Buller HR, van Doormaal FF, van Sluis GL, Kamphuisen PW (2007) Cancer and thrombosis: from molecular mechanisms to clinical presentations. J Thromb Haemost 5(Suppl 1):246–254
2. De BS (1823) lÕObliteration des veines et de son influence sur la formation des hydropisies partielles: consideration sur la hydropisies passive et general. Arch Gen Med 1:188–204
3. Otten HM (2002) Thrombosis and cancer, thesis. Academic Medical Center, University of Amsterdam
4. Trousseau A (1865) Phlegmasia alba dolens. In: Trousseau A (ed) Clinique medicinale de l'Hotel-Dieu de Paris. Bailliere J.-B. et fils, Paris
5. Trousseau A (1877) Ulcere chronique simple de l'estomac. In: Peter M (ed) Clinique Medicinale de lÕHotel-Dieu de Paris. Bailliere J.-B. et fils, Paris
6. Trousseau A (1877) Phlegmasia alba dolens. In: Peter M (ed) Clinique Medicinale de lÕHotel-Dieu de Paris. Bailliere J.-B. et fils, Paris
7. Illtyd JTM (1935) N. Thromboplebitis in cancer. Practitioner 134:683–684
8. Haddad TC, Greeno EW (2006) Chemotherapy-induced thrombosis. Thromb Res 118 (5):555–568
9. Prandoni P, Falanga A, Piccioli A (2005) Cancer and venous thromboembolism. Lancet Oncol 6(6):401–410
10. Rickles FR, Edwards RL (1983) Activation of blood coagulation in cancer: Trousseau's syndrome revisited. Blood 62(1):14–31

11. McLean J (1959) The discovery of heparin. Circulation 19(1):75–78
12. Charles AF, Scott DA (1936) Studies on heparin: observations on the chemistry of heparin. Biochem J 30(10):1927–1933
13. Murray GD, Best CH (1938) The use of Heparin in thrombosis. Ann Surg 108(2):163–177
14. Bauer G (1950) Nine years' experience with heparin in acute venous thrombosis. Angiology 1 (2):161–169
15. Deykin D (1990) Antithrombotic therapy in historical perspective. Am J Cardiol 65(6):2C–6C
16. Barritt DW, Jordan SC (1960) Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial Lancet 1(7138):1309–1312
17. Galanaud JP, Laroche JP, Righini M (2013) The history and historical treatments of deep vein thrombosis. J Thromb Haemost 11(3):402–411
18. Hyers TM (2003) Management of venous thromboembolism: past, present, and future. Arch Intern Med 163(7):759–768
19. van Dongen CJ, van den Belt AG, Prins MH, Lensing AW (2004) Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. Cochrane Database Syst Rev (4):CD001100
20. Prandoni P, Lensing AW, Piccioli A, Bernardi E, Simioni P, Girolami B et al (2002) Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 100(10):3484–3488
21. Ageno W, Steidl L, Marchesi C, Dentali F, Mera V, Squizzato A et al (2002) Selecting patients for home treatment of deep vein thrombosis: the problem of cancer. Haematologica 87(3):286–291
22. Lyman GH, Bohlke K, Khorana AA, Kuderer NM, Lee AY, Arcelus JI et al (2015) Venous thromboembolism prophylaxis and treatment in patients with cancer: american society of clinical oncology clinical practice guideline update 2014. J Clin Oncol 33(6):654–656
23. Meyer G, Marjanovic Z, Valcke J, Lorcerie B, Gruel Y, Solal-Celigny P et al (2002) Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. Arch Intern Med 162(15):1729–1735
24. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M et al (2003) Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 349(2):146–153
25. Deitcher SR, Kessler CM, Merli G, Rigas JR, Lyons RM, Fareed J et al (2006) Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period. Clin Appl Thromb Hemost 12(4):389–396
26. Hull RD, Pineo GF, Brant RF, Mah AF, Burke N, Dear R et al (2006) Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. Am J Med 119(12):1062–1072
27. Lee AYY, Kamphuisen PW, Meyer G, Bauersachs R, Janas MS, Jarner MF et al (2015) Tinzaparin versus Warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. JAMA 314(7):677–686
28. Carrier M, Cameron C, Delluc A, Castellucci L, Khorana AA, Lee AY (2014) Efficacy and safety of anticoagulant therapy for the treatment of acute cancer-associated thrombosis: a systematic review and meta-analysis. Thromb Res 134(6):1214–1219
29. Carrier M, Prandoni P (2017) Controversies in the management of cancer-associated thrombosis. Expert Rev Hematol. 10(1):15–22
30. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H et al (2016) Antithrombotic therapy for VTE disease: CHEST Guideline and Expert Panel Report. Chest 149(2):315–352
31. van der Hulle T, den Exter PL, Kooiman J, van der Hoeven JJ, Huisman MV, Klok FA (2014) Meta-analysis of the efficacy and safety of new oral anticoagulants in patients with cancer-associated acute venous thromboembolism. J Thromb Haemost 12(7):1116–1120

32. Vedovati MC, Germini F, Agnelli G, Becattini C (2015) Direct oral anticoagulants in patients with VTE and cancer: a systematic review and meta-analysis. Chest 147(2):475–483
33. Posch F, Konigsbrugge O, Zielinski C, Pabinger I, Ay C (2015) Treatment of venous thromboembolism in patients with cancer: a network meta-analysis comparing efficacy and safety of anticoagulants. Thromb Res 136(3):582–589
34. Farge D, Bounameaux H, Brenner B, Cajfinger F, Debourdeau P, Khorana AA et al (2016) International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer. Lancet Oncol 17(10):e452–e466
35. Khorana AA, Yannicelli D, McCrae KR, Milentijevic D, Crivera C, Nelson WW et al (2016) Evaluation of US prescription patterns: are treatment guidelines for cancer-associated venous thromboembolism being followed? Thromb Res 145:51–53
36. Streiff MB, Milentijevic D, McCrae K, Yannicelli D, Fortier J, Nelson WW et al (2018) Effectiveness and safety of anticoagulants for the treatment of venous thromboembolism in patients with cancer. Am J Hematol 93(5):664–671
37. Theberge I, Bowdridge J, Forgie MA, Carrier M, Louzada M, Siquiera L et al (2017) Rivaroxaban shows promise as effective therapy for cancer patients with venous thromboembolic disease. Thromb Res 152:4–6
38. Seo S, Ryu M-H, Kang Y-K, Kim K-P, Chang H-M, Ryoo B-Y, Kim SB, Lee J-L, Park SR (2016) Oral rivaroxaban versus subcutaneous low molecular weight heparin treatment for venous thromboembolism in patients with upper gastrointestinal, hepatobiliary and pancreatic cancer. Ann Oncol 27(Suppl 6):695
39. Ross JA, Miller MM, Rojas Hernandez CM (2017) Comparative effectiveness and safety of direct oral anticoagulants (DOACs) versus conventional anticoagulation for the treatment of cancer-related venous thromboembolism: a retrospective analysis. Thromb Res 150:86–89
40. Mantha S, Laube E, Miao Y, Sarasohn DM, Parameswaran R, Stefanik S et al (2017) Safe and effective use of rivaroxaban for treatment of cancer-associated venous thromboembolic disease: a prospective cohort study. J Thromb Thrombolysis 43(2):166–171
41. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D et al (2018) Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 378(7): 615–624
42. Young A, Marshall A, Thirlwall J, Hill C, Hale D, Dunn J et al (2017) Anticoagulation therapy in selected cancer patients at risk of recurrence of venous thromboembolism: results of the select-D pilot trial. In: Ash 59th annual meeting & exposition. Atlanta, GA, p 625. (Blood)
43. Li A, Garcia DA, Lyman GH, Carrier M (2018) Direct oral anticoagulant (DOAC) versus low-molecular-weight heparin (LMWH) for treatment of cancer associated thrombosis (CAT): a systematic review and meta-analysis. Thromb Res. (In press)
44. Lee AY, Peterson EA (2013) Treatment of cancer-associated thrombosis. Blood 122 (14):2310–2317
45. Short NJ, Connors JM (2014) New oral anticoagulants and the cancer patient. Oncologist 19 (1):82–93
46. Noble S, Sui J (2016) The treatment of cancer associated thrombosis: does one size fit all? who should get LMWH/warfarin/DOACs? Thromb Res 140(Suppl 1):S154–S159
47. Noble SI, Finlay IG (2005) Is long-term low-molecular-weight heparin acceptable to palliative care patients in the treatment of cancer related venous thromboembolism? A qualitative study. Palliat Med 19(3):197–201
48. Noble S, Matzdorff A, Maraveyas A, Holm MV, Pisa G (2015) Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica 100(11):1486–1492
49. Khorana AA, Noble S, Lee AYY, Soff G, Meyer G, O'Connell C, Carrier M (2018) Role of direct oral anticoagulants in treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. J Thromb Haemost. (In press)

50. Chee CE, Ashrani AA, Marks RS, Petterson TM, Bailey KR, Melton LJ 3rd et al (2014) Predictors of venous thromboembolism recurrence and bleeding among active cancer patients: a population-based cohort study. Blood 123(25):3972–3978
51. Carrier M, Lazo-Langner A, Shivakumar S, Tagalakis V, Gross PL, Blais N et al (2015) Clinical challenges in patients with cancer-associated thrombosis: canadian expert consensus recommendations. Curr Oncol 22(1):49–59
52. Smith JD, Baillie J, Baglin T, Griffiths GO, Casbard A, Cohen D et al (2014) A feasibility study to inform the design of a randomized controlled trial to identify the most clinically and cost effective anticoagulation length with low molecular weight heparin in the treatment of cancer associated thrombosis (ALICAT): study protocol for a mixed-methods study. Trials 15:122
53. Francis CW, Kessler CM, Goldhaber SZ, Kovacs MJ, Monreal M, Huisman MV et al (2015) Treatment of venous thromboembolism in cancer patients with dalteparin for up to 12 months: the DALTECAN Study. J Thromb Haemost 13(6):1028–1035
54. Jara-Palomares L, Solier-Lopez A, Elias-Hernandez T, Asensio-Cruz M, Blasco-Esquivias I, Marin-Barrera L et al (2017) Tinzaparin in cancer associated thrombosis beyond 6 months: TiCAT study. Thromb Res 157:90–96

8 Etiology and Management of Upper-Extremity Catheter-Related Thrombosis in Cancer Patients

Anita Rajasekhar and Michael B. Streiff

Contents

A. Rajasekhar (✉)
Division of Hematology/Oncology, Department of Medicine, University of Florida, PO Box 100278 1600 SW Archer Rd, Gainesville, FL 32610, USA
e-mail: anita.rajasekhar@medicine.ufl.edu

M. B. Streiff
Division of Hematology, Department of Medicine, Johns Hopkins University School of Medicine, 1830 East Monument Street, Suite 7300, Baltimore, MD 21205, USA

G. Soff (ed.), *Thrombosis and Hemostasis in Cancer*, Cancer Treatment and Research 179, https://doi.org/10.1007/978-3-030-20315-3_8

8.1 Introduction

Central venous access devices (CVADs) are essential to the care of many oncology patients. CVADs facilitate the delivery of cancer chemotherapy, antibiotics, stem cell collection/reinfusion, blood products, and parenteral nutrition and provide venous access for hemodialysis and laboratory blood draws. CVADs can be inserted directly into a central vein or tunneled through subcutaneous tissues for more permanent access or placed peripherally and threaded to a central location (e.g., peripherally inserted central catheters [PICC]). CVAD-related thrombosis (CRT) is the most common non-infectious complication of CVAD insertion. Oncology patients are particularly vulnerable to CRT given their underlying hypercoagulable state. CRT is critical to prevent and treat in a timely manner because it leads to interruptions in therapy, increases the cost of care, and can precipitate chronic venous occlusion and loss of vascular access, post-thrombotic syndrome (PTS), and rarely, pulmonary embolism (PE). However, addressing CRT in cancer patients may be more complex than in the general population given the higher risk of recurrent thrombosis and anticoagulation-associated bleeding experienced by cancer patients. Further, there are limited randomized controlled trials focused on the management of CRT so most recommendations are based upon observational studies or extrapolation from studies of non-CVAD-related lower-extremity deep vein thrombosis (LEDVT). Herein, we highlight the diagnosis and management of CRT in adult cancer patients.

8.2 Pathophysiology

CVADs predispose to venous thrombosis because they adversely influence all three components of Virchow's triad: altered blood flow, hypercoagulability, and endothelial injury. CVAD insertion results in local vessel wall injury activating the coagulation and pro-inflammatory cascades. Continuous friction of CVADs against the vessel wall, as well as turbulent inflow from the catheter and the toxic effects of some medications, promotes ongoing endothelial injury and thrombus formation. In addition, the presence of CVADs in the vessel lumen slows blood flow leading to stasis. Finally, the synthetic materials used to construct CVADs likely activate coagulation as evidenced by the development of fibrin sheaths and catheter-associated thrombus soon after CVAD insertion [1, 2].

Thrombus can form within, surrounding, or at the tip of the catheter (Fig. 8.1). Fibrin sheaths, sock-like structures that deposit on the external surface of the catheter, begin to form within 24 h of insertion and can impair flow into and out of

the catheter [1, 2]. Intraluminal thrombus develops when blood refluxes into the catheter. These occlusions can be partial or complete and result from insufficient flushing, inadequate infusion rates, or frequent blood draws. The majority of fibrin sheaths and intraluminal occlusions can be lyzed with the intraluminal instillation of a thrombolytic agent (i.e., 2 mg of alteplase). Thrombus that forms on the vessel wall adjacent to the CVAD is termed mural thrombus. CRT refers specifically to a DVT that partially or completely occludes the vein in which the catheter resides [1, 2].

8.3 Epidemiology and Risk Factors for CRT

The concept that upper-extremity DVT (UEDVT) is rare and clinically insignificant is being revaluated. Recent studies report that the incidence of UEDVT has more than doubled from <2 to 4–10% of all newly diagnosed DVT [1–6]. Secondary events after UEDVT including pulmonary embolism, recurrent VTE, and post-thrombotic syndrome appear to be less frequent than with LEDVT [7]. The presence of CVAD is a strong independent risk factor for UEDVT (OR 14.0; 95% CI 5.9–33.2), and CRT accounts for 50–90% of all UEDVT [3, 5, 6, 8]. The incidence of CRT has been estimated at 0.4–1.0 per 10,000 persons in the general population with the majority of CRT occurring within 100 days of catheter placement [9, 10]. CRT is particularly common in cancer patients in whom the frequency of CRT has been estimated to be 5–10% [11–15]. A recent study of 5043 central lines inserted in 3218 cancer patients found that the overall incidence of CRT was 3.55% at a rate of 0.45 per 1000 line days [16].

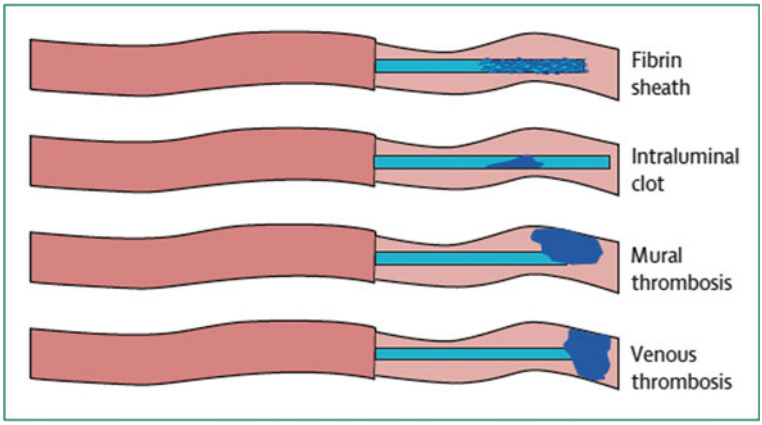

Fig. 8.1 Type of CVAD-related thrombotic occlusions. Permission from Baskin et al. [2]

Table 8.1 Potential risk factors for CRT

Device-related factors	Patient-related factors	Treatment-related factors
Multiple insertion attempts [9]	Malignancy Metastatic > localized [17, 28]	Ongoing cancer therapy [4, 29, 30] Radiation therapy to the chest [17] Bolus (vs. diluted) chemotherapy infusions [18] Antiangiogenic agents and platinum therapy [31]
Catheter insertion site (femoral > jugular > subclavian) [8, 25, 27, 28, 32]	Recent trauma/surgery within 30 days [5, 20]	Erythrocyte-stimulating agents [28]
Large catheter size-to-vein-diameter ratio [4, 7]	History of VTE [20, 32]	Parenteral nutrition [21]
CVT subtype (PICC > centrally inserted catheter > implanted port) [4, 8, 32, 33]	End-stage renal disease [4, 20, 22]	Surgery [30]
Catheter infection [34]	Critically ill patients [33]	
Improper catheter position (not at atriocaval junction) [32]	Systemic or catheter-related infection [5, 34]	
Number of lumens and catheter size (6F triple-lumen > 5F double-lumen > 4F single-lumen) [20, 29, 28]	Older age [27]	
CVAD material (polyethylene or polyvinylchloride > silicone or polyurethane) [23]	Immobilization within 30 days [5]	
Previous CVAD [8, 28]	Inherited thrombophilia [24, 28, 35]	

Variability in the reported risk factors for CRT exists due to differences in study design, patient population, use of thromboprophylaxis, and outcome assessment. Risk factors for CRT can be grouped into device-related, patient-related, and treatment-related factors (Table 8.1) [7, 8, 17–23]. CRT risk varies by insertion site with the femoral vein being the highest risk site followed by the jugular and subclavian veins. In a multicenter, randomized controlled trial (RCT) of 3027 adult ICU patients and 3471 CVAD insertions, symptomatic DVT was diagnosed more frequently with femoral vein catheters versus subclavian catheters (15 vs. 5, hazard ratio [HR] 3.4 [95% CI 1.2–9.3]) and jugular catheters (20 vs. 9, HR 2.4 [95% CI 1.1–5.4]) (pairwise comparisons) [24]. Similar findings have been noted in some studies [25, 26] but not all [27]. In their patient data-level meta-analysis of 5636 subjects with 425 CRT, Saber et al. found that a subclavian insertion site was associated with a twofold increased risk of CRT compared to an upper arm insertion site [27]. Unlike the previous studies, the Saber meta-analysis focused only on studies of cancer patients which primarily used tunneled Hickman catheters, ports, and PICCs as opposed to non-tunneled central lines. In addition,

only upper-extremity sites were used in the included studies and the median duration of insertion was 15–237 days compared to 5–11 days in the previous studies [24–27].

A meta-analysis of 11 studies found that PICCs were associated with a 2.5-fold higher risk of DVT than centrally inserted venous catheters [32]. Implanted ports were associated with a significantly lower risk for CRT compared with PICCs (odds ratio [OR] 0.43 [95% CI 0.23–0.80]) [27]. Larger PICCs (6 French [F] triple-lumen 8.8% > 5F double-lumen 2.9% > 4F single-lumen 0.6%) and brachial and cephalic vein insertion sites are associated with a greater risk for symptomatic CRT [4, 33]. Catheter tips dwelling above the proximal superior vena cava have a sevenfold higher risk of CRT compared with catheter tips located closer to the right atrium [27, 29]. An indwell time exceeding 2 weeks also increases the risk of CRT [36].

Patient-related factors also influence CRT risk. Older age and body mass index have been associated with increased risk, while gender and ethnicity have not [26, 34]. Cancer and ICU patients are at increased risk as are patients with CVAD-related infections [30, 32, 34]. UEDVT is associated with cancer in 40% of cases [37]. Unfortunately, treatment of UEDVT in cancer patients remains challenging due to a two–threefold higher risk for recurrent VTE, eightfold increased risk of mortality, and fourfold increased risk of bleeding compared to non-cancer patients [38]. In cancer patients, age <50 (HR 1.46, 95% CI 1.06–2.00, $p = 0.019$) and the number of prior CRT (HR 1.95, 95% CI 1.30–2.92, $p = 0.01$) have been associated with higher thrombosis rates; however, cancer subtype and insertion side were not predictive [16]. The presence of inherited thrombophilia as well as a personal history of VTE increases the risk of CRT [4, 27, 33, 39]. Treatment-related risk factors for CRT include chemotherapy and surgery while therapeutic anticoagulation reduces the risk of thrombosis (Relative risk [RR] 0.47; 95% CI, 0.23–0.99) [4, 26, 33, 34].

8.4 Prevention of CRT

Prevention practices should target patient-, treatment-, and device-related risk factors for CRT. For example, clinicians should utilize the smallest caliber catheter possible, ensure proper catheter tip location, and remove CVADs when they are no longer needed. Measures to prevent catheter-related infections can reduce CRT risk. Although flushing or locking catheters with heparin or saline has been standard practice for years, data demonstrating the effectiveness of these practices are lacking [35]. Anticoagulant thromboprophylaxis to prevent CRT has been the subject of multiple clinical trials [40–52]. Early studies suggested that fixed-low-dose warfarin (1 mg daily) or LMWH (dalteparin 2500 units daily) was associated with reduced rates of CRT in cancer patients [40, 41]. However, more recent larger prospective RCTs have failed to confirm these benefits [46–48].

Table 8.2 Summary of clinical guideline recommendations for the prevention and treatment of CRT

Guideline	Prevention	Treatment
[a]ACCP 2012 [55], 2016 [60]	• In outpatients with cancer and indwelling CVAD, suggest against routine prophylaxis with LMWH or LDUH (Grade 2B) or vitamin K antagonists (VKA) (Grade 2C)	• In patients with acute UEDVT – Recommend parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no anticoagulation (Grade 1B) – Suggest LMWH or fondaparinux over IV UFH (Grade 2C) and over SC UFH (Grade 2B) – Suggest anticoagulant therapy alone over thrombolysis (Grade 2C) • If thrombolysis is administered, recommend the same intensity and duration of anticoagulant therapy compared to non-thrombolysis patients (Grade 1B) • Suggest that the CVAD not be removed if it is functional and there is an ongoing need for the catheter (Grade 2C) • If CVAD is removed, 3 months of anticoagulation is recommended over a longer duration of therapy in non-cancer patients (Grade 1B). The same approach is suggested in cancer patients (Grade 2C) • If CVAD is not removed, anticoagulation is recommended over stopping after 3 months of treatment in cancer patients (Grade 1C). The same approach is suggested in non-cancer patients (Grade 2C)
ASCO 2013 [57, 61]	• In cancer patients with CVADs – Routine thromboprophylaxis is not recommended – Routine CVAD flushing with saline is recommended – Data are insufficient to recommend routine thrombolytics to prevent catheter occlusion	• In cancer patients with CRT – t-PA is recommended to restore patency and preserve catheter function – CVAD removal is recommended if thrombosis does not respond to fibrinolytic therapy or if fibrinolytic or anticoagulation therapy is contraindicated – 3 to 6 months of anticoagulant therapy with LMWH or LMWH followed by warfarin (INR, 2.0–3.0) is recommended for treatment of symptomatic CRT
[b]ESMO, 2015 [59]	• In cancer patients with CVADs – Routine thromboprophylaxis is not recommended	• In cancer patients with CRT – LMWH is preferred over VKA [II, A]

(continued)

Table 8.2 (continued)

Guideline	Prevention	Treatment
	– Prophylaxis with thrombolytic agents is not recommended [I,A] – Saline flushing is recommended [III, C]	– Anticoagulation treatment should be continued for the time length of time the catheter is in use [III, C] – If CVAD is non-functional, the CVAD should be removed after a short course (3–5 days) of anticoagulation [I, A] – LMWH alone or LMWH followed by warfarin should be used for a minimum of 3–6 months [I, C] – After treatment of CRT, prophylactic doses of anticoagulation should be continued as long as the CVAD remains indwelling [I, C] – Thrombolytic therapy is not routinely recommended [I,B]
[c]International Guideline 2013 [62]	• In cancer patients with CVADs – Routine thromboprophylaxis is not recommended [Grade 1A]. – Catheters should be inserted on the right side, in the jugular vein, with catheter tip in the junction of the superior vena cava and the right atrium [Grade 1A]	• In cancer patients with CRT – Anticoagulation is recommended for a minimum 3 months – LMWHs are suggested but VKA can also be used – CVAD removal is not required if functional, well positioned, and not infected – Whether or not the CVAD is removed, no standard approach in terms of duration of anticoagulation is established [best clinical practice]
[d]NCCN 2015 [58]	• In cancer patients with CVADs – Routine thromboprophylaxis is not recommended (GRADE 2A)	• In cancer patients with CRT – Anticoagulation is recommended for as long as the CVAD remains indwelling – If the CVAD is removed, at least 3 months of anticoagulation is recommended – Consider CVAD removal if symptoms persist, CVAD is non-functional or no longer necessary – Consider catheter-directed thrombolysis in select cases

[a]Levels of evidence and grades of recommendation adapted from the ACCP-modified GRADE approach [63]

[b]Levels of evidence and grades of recommendation adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System

[c]Levels of evidence and grades of recommendations utilized the international GRADE approach [64, 65]

[d]Levels of evidence and grading of recommendations based on the NCCN categories of evidence and consensus [66]

The WARP study, a large open-label multicenter RCT of CVAD thromboprophylaxis in cancer patients, found that fixed-low-dose warfarin (1 mg daily) did not reduce the rate of CRT (RR 0.99, 95% CI 0.57–1.72) compared to no warfarin [51]. However, dose-adjusted warfarin (INR 1.5–2.0) was associated with a significant reduction in CRT (RR 0.38, 95% CI 0.20–0.71) compared to fixed-dose warfarin, albeit at the cost of a trend toward increased major bleeding (3.4% vs. 1.5%, OR 2.28, 95% CI 0.95–5.48, $p = 0.09$) [51]. Randomized controlled trials comparing LMWH with placebo have not demonstrated any benefit of thromboprophylaxis [46, 48, 49]. A meta-analysis of CVAD thromboprophylaxis in cancer patients noted a reduction in symptomatic DVT with heparin and a reduction in asymptomatic DVT with vitamin K antagonists but no impact on infections, bleeding, or mortality with low-to-moderate quality of evidence due to heterogeneous patient populations and low event rates [53]. More recently, a multi-disciplinary expert panel concluded in the FOTROCON Delphi consensus statement that the systematic use of thromboprophylaxis to prevent CRT was not indicated [54]. Taken together, current evidence-based guidelines do not recommend routine thromboprophylaxis for cancer or non-cancer patients with CVADs [55–59] (Table 8.2). In our practice, we do not routinely use thromboprophylaxis in cancer patients with CVADs beyond standard catheter care including use of heparin or saline flushes.

8.5 Presentation

The majority of CRT are asymptomatic or present with CVAD dysfunction (inability to infuse or aspirate from the catheter) or fever from a CVAD-associated infection. Symptomatic CRT occurs in 1–5% of patients and typically presents with discomfort, edema, or discoloration at the catheter insertion site or in the ipsilateral upper extremity. Venous collaterals may be visible in the neck, arm, or chest. Septic thrombophlebitis can herald progression to CRT. Therefore, clinicians should examine the catheter entry site for signs of CVAD-related infection. CVADs are the most common non-malignant cause of SVC syndrome, so facial or neck swelling, plethora, pain, headaches, or head fullness should prompt investigation for CRT [1, 2, 35].

8.6 Diagnosis

Clinical diagnosis of CRT is unreliable [67]. To standardize and optimize the clinical evaluation, Constans et al. developed a clinical prediction rule to assess the pre-test probability of UEDVT [68]. The Constans clinical decision score uses a combination of four factors that were found to be associated with the risk of UEDVT. The presence of an intravenous device (pacemaker or central venous catheter) (1 point), localized pain (1 point), unilateral edema (1 point), or an alternative plausible cause for symptoms (−1 point) is used to calculate the

Constans score. In a prospective management study of 406 patients, an unlikely Constans clinical decision score (0–1 point) in conjunction with a negative D-dimer was associated with a failure rate of 0% at 3-month follow-up (95% CI 0.0% to 4.2%) [69]. If these results are confirmed, this algorithm may become the standard diagnostic approach to UEDVT.

Although the reference standard for diagnosis of UEDVT is contrast venography, venous duplex ultrasonography remains the first-line diagnostic test for CRT. A systematic review of 793 patients from 17 studies with UEDVT reported a sensitivity and specificity of 97 and 96% for compression ultrasound, 84 and 94% for Doppler ultrasound, and 91 and 93% for duplex ultrasound, although the studies were small and heterogeneous [70]. Since the thoracic cavity and clavicle interfere with Doppler flow assessment and compression of the brachiocephalic and subclavian vein and the superior vena cava, CT venography (CTV) should be considered in patients with a negative ultrasound and high clinical suspicion. In patients with suspected UEDVT, the American College of Chest Physicians (ACCP) guideline recommends duplex ultrasound over other initial tests, including highly sensitive D-dimer or venography (Grade 2C). If the ultrasound is negative and clinical suspicion remains high, further testing with D-dimer, serial duplex ultrasound, or venography is advocated (Grade 2C) [71].

8.7 Treatment

The rationale for treatment of CRT is to reduce symptoms, prevent/eliminate catheter dysfunction, minimize the risk of progressive or recurrent thromboembolism, and prevent PTS. Treatment strategies include catheter removal, anticoagulation, catheter-directed pharmacomechanical thrombolysis/thrombectomy, or surgical thrombectomy. Given the lack of level 1 data, recommendations are largely based on the results of LEDVT/PE treatment trials in cancer and non-cancer patients.

8.7.1 Anticoagulation

The preferred treatment of CRT is anticoagulation alone. In 74 cancer patients with CRT, Kovacs et al. found that treatment with dalteparin transitioned to warfarin (INR 2–3) without catheter removal was associated with no episodes of recurrent thromboembolism and only three episodes of major bleeding (4%) [72]. Delluc et al. reported similar outcomes in 89 cancer patients with CRT treated with dalteparin alone (200 units/kg daily for 1 month followed by 150 units/kg daily). During a median duration of anticoagulation of 124 days (range: 40–1849 days), there were no recurrent DVT/PE occurred and only two major bleeds (3.7 per 100 patient-years [95% CI: −0.1 to 9.0]) were reported [73]. In a systematic review of

Table 8.3 Authors' recommendations for management of central venous access device (CVAD)-related thrombosis (CRT)

Clinical indication
Prevention
Place CVAD in subclavian > jugular > femoral insertion site
Place port > Hickman > PICC
Place smallest caliber catheter feasible
Place catheter tip at SVC-RA junction
Do not use anticoagulant thromboprophylaxis
Diagnosis
Ultrasound to confirm suspected thrombosis
No ultrasound surveillance
CT (or MR) venography to confirm suspected thrombosis in patients with negative venous ultrasound
Treatment
Anticoagulation for 3 months or until CVAD removed (whichever is longer)
Thrombolysis for limb-threatening CRT or severe symptoms and failure to respond to AC
CVAD removal if AC contraindicated or infected or no longer needed (add AC once CI resolves)
Avoid SVC filter use
Graduated compression garment for symptomatic upper-extremity PTS but not PTS prevention

CVAD central venous access device; *PICC* peripherally inserted central catheter; *SVC-RA* superior vena cava-right atrium junction; *CT* computed tomography; *MRI* magnetic resonance imaging; *CRT* catheter-related thrombosis; *AC* anticoagulation; *CI* contraindication; *PTS* post-thrombotic syndrome

CRT, 7% experienced recurrent UE or LEDVT and 2.8% suffered a PE. Major hemorrhage occurred in 4.9% of patients [28].

These data and results from RCTs of LEDVT and/or PE treatment provide the evidence basis for current guidelines (Table 8.2) [56–62]. Agreement among the guidelines exists with regard to initial anticoagulation for CRT involving proximal upper-extremity deep veins (e.g., axillary, subclavian, etc.) rather than CVAD removal unless anticoagulation is contraindicated. While thromboembolic complications associated with DVTs distal to the axillary vein (e.g., brachial vein) are less frequent, if the catheter is not removed clinicians should strongly consider using at least prophylactic doses of anticoagulation to prevent thrombus progression. If the CVAD is removed, clinical surveillance without anticoagulation may be an option for a distal arm vein DVT.

The ACCP 2016 guidelines give a Grade 2B recommendation for the new oral anticoagulants over vitamin K antagonist (VKA) therapy in non-cancer patients with VTE based on the greater convenience and accumulating evidence that direct oral anticoagulants (DOACs) have similar efficacy in non-cancer patients and an

improved adverse event profile, particularly less intracranial bleeding. For non-cancer patients not treated with a DOAC, VKA therapy is still recommended over low-molecular weight heparin (LMWH) (Grade 2C) [60] (Table 8.3).

In cancer patients with VTE, all major evidence-based guidelines recommend LMWH as the primary choice of anticoagulant and VKA as an inferior alternative [56–62]. Although LMWH is the preferred agent for CRT in cancer patients, a LMWH bridge to warfarin is an acceptable option [72]. It should be noted that trials showing superiority of LMWH over VKA for cancer-associated thrombosis excluded UEDVT patients, and specifically those with CRT. If upper-extremity symptoms fail to improve with anticoagulation or there is a catheter-associated infection, then CVAD removal should be considered. The guidelines recommend a minimum of 3 months of anticoagulation for CRT over shorter or longer durations, regardless of CVAD removal. If the CVAD is not removed, then anticoagulation should continue as long as the CVAD remains in place rather than stopping after 3 months of treatment [56–62].

However, due to the need for daily subcutaneous injections, discontinuation rates of long-term LMWH in cancer patients are as high as 58 and 11–20% of cancer patients prefer to switch to oral anticoagulation within the first 3–6 months of treatment to avoid injections [74–79]. In fact in one prospective multicenter cohort study, one in five cancer patients with VTE stopped LMWH because of side effects [80]. The unique burden associated with long-term use of a parenteral anticoagulant is important to consider in light of trials examining direct oral anticoagulants for the prevention and treatment of cancer-associated VTE. Since the publication of the key evidence-based guidelines advocating the use of DOACs in non-cancer patients with VTE, more data on the use of DOACs in the treatment of cancer-associated thrombosis have become available. Four recent meta-analyses of large RCT trials evaluating DOACs in the treatment of VTE suggest efficacy and safety of DOACs in cancer patients [81–84]. However, these meta-analyses are limited by the small percentage of cancer patients (6–9%) enrolled in these RCTs and the fact that patients with CRT were excluded. Further, since all the studies compared only VKA to DOACs, no head-to-head comparisons of DOACs to LMWH were available to inform these meta-analyses. The network meta-analysis of Posch et al. provides indirect estimates of the comparative effectiveness of LMWH to DOACs in cancer patients with thrombosis [85]. DOACs provided comparable efficacy to LMWH (RR = 1.08, 95% CI: 0.59–1.95, $p = 0.81$) and a non-significant trend toward improved safety (RR = 0.67, 95% CI: 0.31–1.46, $p = 0.31$). Recently, two randomized controlled trials (Select-d and HOKUSAI-VTE Cancer) which compared dalteparin to a DOAC (rivaroxaban and edoxaban, respectively) for long-term treatment of cancer-associated VTE were reported. Both showed a trend toward a lower incidence of recurrent VTE but a higher risk of bleeding, specifically gastrointestinal (GI) bleeding [86, 87]. A recent meta-analysis including these two RCTs revealed that DOACs had a lower 6-month recurrent VTE event rate compared with LMWH (RR 0.65; 95% CI 0.42–1.01), but a higher rate of major bleeding (RR 1.74; 95% CI 1.05–2.88) and clinically relevant

non-major bleeding (CRNMB) (RR 2.31; 95% CI 0.85–6.28) with no difference in mortality (RR 1.03; 95% CI 0.85–1.26) [88].

Few studies have addressed DOACs as treatment for cancer-associated CRT. A single-center retrospective study reviewed the outcome of 83 cancer patients treated with rivaroxaban for CRT [89]. The majority of patients (73%) had advanced stage cancer. Approximately half had an incidentally discovered CRT. Ninety-three percent of events were associated with a port. At 90 days, there were six deaths (unclear causes), three recurrent VTE at different locations, two major bleeds (2.4%), and one CRNMB that led to discontinuation of rivaroxaban. Only 3.6% of patients required catheter removal due to line dysfunction [89]. The catheter 2 study was a multicenter prospective cohort study which treated 70 cancer patients with CRT with rivaroxaban [90]. After 12 weeks of therapy, line function was preserved in 100% of subjects, one suffered recurrent VTE (1.43%; fatal PE), and seven suffered major bleeding (10%). Bleeding events tended to occur in the GI and genitourinary (GU) tracts [90]. The high rate of bleeding over a short follow-up period raises safety concerns particularly in patient with GI or GU malignancies. Further investigation of DOACs is warranted to determine their role in the treatment of CRT.

8.7.2 Catheter Removal

Catheter removal is an acceptable alternative to anticoagulation particularly in patients who no longer need central venous access or are at high risk of bleeding [56–62]. When acute thrombus is adherent or in close approximation to the catheter, there is understandable concern about clot embolization upon CVAD removal. Unfortunately, the available literature does not permit an evidence-based recommendation regarding the need for anticoagulation and the minimal duration of therapy required to reduce the frequency of embolization. However, we suggest a short course of therapeutic anticoagulation (at least 7 days, if possible) prior to CVAD removal as the first week after diagnosis is associated with the highest risk of recurrent thromboembolism [91]. Given that this suggestion is based upon data on the treatment of LEDVT/PE, we encourage decision-making in this regard be made on a case-by-case basis depending upon the location and size of the thrombus, the risk for embolization and its related sequelae, and the potential complications resulting from delayed removal (i.e., CVAD-associated sepsis). Reasons to consider early catheter removal include catheter dysfunction, concomitant CVAD-related infection, or failure of symptoms to resolve with anticoagulation alone [1, 6]. After CVAD removal, at least 3 months of anticoagulation is recommended [56–62].

8.7.3 Superior Vena Cava (SVC) Filters

In patients with absolute contraindications to anticoagulation, some have recommended insertion of a SVC filter. At present, no vena cava filter has been specifically approved for deployment in the SVC. When utilized, an SVC filter is placed at the junction of the left and right brachiocephalic veins. SVC filters are associated with a significant risk of major complications including SVC perforation, cardiac tamponade, SVC thrombosis, aortic perforation, and pneumothorax [92]. This risk when combined with the relative infrequency of PE associated with UEDVT suggests that filters should not be used for CRT except in the most extreme circumstances. This suggestion is particularly valid for cancer patients who are inherently hypercoagulable and presumably at higher risk for thrombotic complications. Instead, CVAD removal should be considered. In patients with acute proximal lower-extremity CRT and an absolute contraindication to anticoagulation, an inferior vena cava filter can be considered.

8.7.4 Thrombolysis

The goal of catheter-directed thrombolysis (CDT) with or without the use of percutaneous mechanical thrombectomy devices (PMT) is to prevent limb loss in patients presenting with acute limb ischemia, facilitate the rapid relief of symptoms (particularly in patients whose symptoms have not resolved with anticoagulation), and reduce the incidence or severity of PTS. However, these benefits must be weighed against the increased risk for major bleeding. Support for the efficacy of CDT ± PMT comes primarily from studies of extensive LEDVT. In patients with acute LEDVT, successful lysis of thrombus can be achieved in 80–90% subjects with CDT [93]. In the CAVENT study, patients with acute proximal LEDVT randomized to CDT had a 26% lower risk of PTS at 2 years compared with anticoagulation alone (41.1% vs. 55.6%; P 5.04); however, these patients also had a 3.2% increased risk of major bleeding [94]. At 5 years, the reduction in PTS was greater between the two groups (43% vs. 71%; $P < 0.001$); however, there was no difference in quality of life scores after 6 months [95]. In patients with acute UEDVT treated with CDT, one retrospective study demonstrated >90% clot lysis in 20 (67%) patients and >50% clot lysis in 29 (97%) patients. No PE occurred but major bleeding developed in 3 (10%) patients [96]. In a retrospective series of 68 patients with UEDVT (33 associated with CVAD, 35 with cancer), Maleux et al. reported 88.6% clot lysis in the cancer patients and major bleeding in 1 (fatal intracranial bleed in a patient with metastatic cancer) [97]. Using a regional infusion of urokinase (75–150,000 units/hour for 24–96 h), Schindler et al. treated 18 patients undergoing high-dose chemotherapy with or without autologous stem cell transplant who developed upper-extremity CRT. Eight patients (44%) developed complete resolution of symptoms and 9 (50%) achieved 50% or greater clot lysis.

One patient (5.6%) suffered a major GI bleed [98]. More recently, the results of the multicenter randomized ATTRACT trial showed that addition of pharmacomechanical CDT to systemic anticoagulation alone did not result in a lower risk of the post-thrombotic syndrome (47% CDT vs. 48% anticoagulation, $p = 0.56$) but was associated with a higher risk of short-term major bleeding (1.7% CDT vs. 0.3% anticoagulation, $P = 0.049$) compared to anticoagulation alone. The severity of PTS and symptoms of leg pain and swelling were reduced by CDT; however, quality of life was similar in the two groups of patients. It is important to note that this study included only acute proximal LEDVT. No patients had CRT, and active cancer patients were excluded [31].

These data suggest that CDT ± PMT should not be routinely used for acute DVT, whether catheter-related or not. Carefully selected cancer patients with acute limb ischemia can be considered for CDT, with particular attention to bleeding risk in this population. The 2016 ACCP guidelines recommend anticoagulant therapy alone over thrombolysis in patients with acute UEDVT that involves the axillary or more proximal veins (Grade 2C). In patients who meet all the following criteria, thrombolysis can be considered: severe symptoms, extent of thrombus from subclavian to axillary vein, symptoms <14 days, good performance status, life expectancy ≥1 year, and low risk for bleeding [60]. Risk factors for bleeding include recent or active bleeding, recent major surgery/trauma, hepatic dysfunction, thrombocytopenia, a bleeding disorder, cardiopulmonary resuscitation, and lesions in organs at high risk for life-threatening bleeding (e.g., brain metastasis). In selecting patients for CDT ± PMT careful attention must be paid to the risk/benefit profile of each patient. The timing of thrombolysis should be determined on a case-by-case basis weighing the severity and extent of the patient's clot and their risk of bleeding. The duration and intensity of anticoagulation for CRT remain the same regardless of whether CDT ± PMT is undertaken or not (Grade 1B) [60].

8.8 Complications of CRT

CRT is associated with a number of clinically relevant complications including catheter dysfunction, recurrent DVT, PE, PTS, and anticoagulation-associated bleeding. An analysis of recurrent VTE and bleeding outcomes in patients with CRT included in the RIETE registry revealed that cancer was the leading risk factor associated with CRT (65% of 558 patients with CRT) [99]. The rate of recurrent (UE and LE) DVT during and after therapy was 2.83 and 2.88 per 100 patient-years, respectively [99]. An important long-term consequence of recurrent CRT is the loss of central venous access, which can have significant implications for cancer patient care and outcomes. Although PE is 4.6-fold more common with LEDVT than UEDVT, the frequency of symptomatic PE associated with UEDVT was 5.4% in one review of the literature [92]. Among 558 patients with CRT in the RIETE registry, 45 (8.1%) were associated with initial symptomatic PE including 1 fatal PE [99].

Risk factors for recurrent DVT/PE among patients with CRT in the RIETE registry included PE at presentation (hazard ratio [HR] 2.41 [90% CI 0.98–5.94]) and a creatinine clearance <60 ml/min (HR 3.93 [2.00–7.70]). Age >65 years (HR 0.23 [0.10–0.54]) and a duration of anticoagulation >90 days (HR 0.23 [0.10–0.56]) were associated with a reduced risk of recurrent VTE while the presence of transient risk factors was associated with a reduced risk of recurrent DVT (HR 0.07 [0.01–0.45]). Interestingly, cancer patients had a 60% less or recurrent VTE compared with patients without risk factors for CRT. Most recurrent thrombotic events occurred within the first 2 months of therapy. After completion of anticoagulation, recurrent DVT/PE occurred at a rate of 1.4–1.8% per year [99].

CRT is also complicated by PTS. A 2006 meta-analysis found that the weighted mean frequency of PTS after UEDVT was 15% (range 7–46%). Risk factors for PTS after UEDVT include residual thrombosis on ultrasound (HR 4.0 [95% CI 1.1–15.0]) and involvement of the axillary and subclavian veins (HR 2.9 [95% CI 0.8–10.7]). CRT may be associated with a lower risk of PTS compared with other UEDVT [100]. The 2016 ACCP guideline does not recommend the use of graduated compression stockings, sleeves, or bandages for patients with acute symptomatic UEDVT. However, in light of the limited data on the utility of these measures in patients with UEDVT, clinicians may consider these strategies in select patients in whom their benefits are judged to exceed their harms and costs (Grade 2C) [60].

8.9 Conclusion

Central venous access device-related thrombosis (CRT) is an increasingly common cause of venous thromboembolism. To reduce the risk of CRT, clinicians should use CVADs only when necessary and minimize patient exposure to known risk factors for thrombosis. Cancer patients are particularly high risk for thrombosis in general and CRT in particular. Currently, there is no indication for routine anticoagulant thromboprophylaxis in patients with CVADs. Ultrasound remains the preferred imaging modality for objective confirmation of CRT. Anticoagulation without CVAD removal remains the preferred approach to treatment. CVAD removal is appropriate when symptoms fail to resolve with anticoagulation or when the device is no longer needed or catheter-related bacteremia is present. Thrombolysis should be reserved for patients at low risk for bleeding who have extensive, limb-threatening thrombosis, or persistence of severe symptoms despite a trial of anticoagulation. SVC filters are likely associated with more complications than benefits and thus are not recommended.

References

1. Rajasekhar A, Streiff MB (2017) How I treat central venous access device-related upper extremity deep vein thrombosis. Blood 129:2727–2736

2. Baskin JL, Pui CH, Reiss U et al (2009) Management of occlusion and thrombosis associated with long-term indwelling central venous catheters. Lancet 374(9684):159–169
3. Munoz FJ, Mismetti P, Poggio R et al (2008) Clinical outcome of patients with upper-extremity deep vein thrombosis: results from the RIETE registry. Chest 133:143–148
4. Evans RS, Sharp JH, Linford LH et al (2010) Risk of symptomatic DVT associated with peripherally inserted central catheters. Chest 138:803–810
5. Joffe HV, Kucher N, Tapson VF, Goldhaber SZ (2004) Deep vein thrombosis (DVT) FREE steering committee. Upper-extremity deep vein thrombosis: a prospective registry of 592 patients. Circulation 110:1605–1611
6. Winters JP, Callas PW, Cushman M, Repp AB, Zakai NA (2015) Central venous catheters and upper extremity deep vein thrombosis in medical inpatients: the medical inpatients and thrombosis (MITH) study. J Thromb Haemost 13:2155–2160
7. Kucher N (2011) Clinical practice. Deep-vein thrombosis of the upper extremities. N Engl J Med 364:861–869
8. Lee JA, Zierler BK, Zierler RE (2012) The risk factors and clinical outcomes of upper extremity deep vein thrombosis. Vasc Endovascular Surg 46:139–144
9. Lee AY, Levine MN, Butler G et al (2006) Incidence, risk factors, and outcomes of catheter-related thrombosis in adult patients with cancer. J Clin Oncol 24:1404–1408
10. Linnemann B, Lindhoff-Last E (2012) Risk factors, management and primary prevention of thrombotic complications related to the use of central venous catheters. Vasa 41:319–332
11. Monreal M, Raventos A, Lerma R et al (1994) Pulmonary embolism in patients with upper extremity DVT associated to venous central lines—a prospective study. Thromb Haemost 72:548–550
12. Baarslag HJ, van Beek EJ, Koopman MM, Reekers JA (2002) Prospective study of color duplex ultrasonography compared with contrast venography in patients suspected of having deep venous thrombosis of the upper extremities. Ann Intern Med 136:865–872
13. Verso M, Agnelli G (2003) Venous thromboembolism associated with long-term use of central venous catheters in cancer patients. J Clin Oncol 21:3665–3675
14. De Cicco M, Matovic M, Balestreri L et al (1997) Central venous thrombosis: an early and frequent complication in cancer patients bearing long-term silastic catheter. A prospective study. Thromb Res 86:101–113
15. Walshe LJ, Malak SF, Eagan J, Sepkowitz KA (2002) Complication rates among cancer patients with peripherally inserted central catheters. J Clin Oncol 20:3276–3281
16. Ellis M, Okano S, McCann A et al (2017) Catheter-related thrombosis incidence and risk factors in adult cancer patients with central venous access devices. Blood 130:2096
17. Verso M, Agnelli G, Kamphuisen PW et al (2008) Risk factors for upper limb deep vein thrombosis associated with the use of central vein catheter in cancer patients. Intern Emerg Med 3:117–122
18. Baglin TP, Boughton BJ (1986) Central venous thrombosis due to bolus injections of antileukaemic chemotherapy. Br J Haematol 63:606–607
19. Malinoski D, Ewing T, Bhakta A et al (2013) Which central venous catheters have the highest rate of catheter-associated deep venous thrombosis: a prospective analysis of 2,128 catheter days in the surgical intensive care unit. J Trauma Acute Care Surg 74:454–460 (discussion 461–2)
20. Nifong TP, McDevitt TJ (2011) The effect of catheter to vein ratio on blood flow rates in a simulated model of peripherally inserted central venous catheters. Chest 140:48–53
21. Marnejon T, Angelo D, Abu Abdou A, Gemmel D (2012) Risk factors for upper extremity venous thrombosis associated with peripherally inserted central venous catheters. J Vasc Access 13:231–238
22. Gallieni M, Pittiruti M, Biffi R (2008) Vascular access in oncology patients. CA Cancer J Clin 58:323–346

23. Martinelli I, Battaglioli T, Bucciarelli P, Passamonti SM, Mannucci PM (2004) Risk factors and recurrence rate of primary deep vein thrombosis of the upper extremities. Circulation 110:566–570
24. Parienti JJ, Mongardon N, Megarbane B et al (2015) Intravascular complications of central venous catheterization by insertion site. N Engl J Med 373:1220–1229
25. Merrer J, De Jonghe B, Golliot F et al (2001) Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. JAMA 286:700–707
26. Timsit JF, Farkas JC, Boyer JM et al (1998) Central vein catheter-related thrombosis in intensive care patients: incidence, risks factors, and relationship with catheter-related sepsis. Chest 114:207–213
27. Saber W, Moua T, Williams EC et al (2011) Risk factors for catheter-related thrombosis (CRT) in cancer patients: a patient-level data (IPD) meta-analysis of clinical trials and prospective studies. J Thromb Haemost 9:312–319
28. Baumann Kreuziger L, Onwuemene O, Kolesar E, Crowther M, Lim W (2015) Systematic review of anticoagulant treatment of catheter-related thrombosis. Thromb Res 136:1103–1109
29. Luciani A, Clement O, Halimi P et al (2001) Catheter-related upper extremity deep venous thrombosis in cancer patients: a prospective study based on Doppler US. Radiology 220:655–660
30. van Rooden CJ, Schippers EF, Barge RM et al (2005) Infectious complications of central venous catheters increase the risk of catheter-related thrombosis in hematology patients: a prospective study. J Clin Oncol 23:2655–2660
31. Vedantham S, Goldhaber SZ, Julian JA et al (2017) Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. N Engl J Med 377:2240–2252
32. Chopra V, Anand S, Hickner A et al (2013) Risk of venous thromboembolism associated with peripherally inserted central catheters: a systematic review and meta-analysis. Lancet 382:311–325
33. Chopra V, Fallouh N, McGuirk H et al (2015) Patterns, risk factors and treatment associated with PICC-DVT in hospitalized adults: a nested case-control study. Thromb Res 135:829–834
34. Leung A, Heal C, Perera M, Pretorius C (2015) A systematic review of patient-related risk factors for catheter-related thrombosis. J Thromb Thrombolysis 40:363–373
35. Geerts W (2014) Central venous catheter-related thrombosis. Hematology Am Soc Hematol Educ Program 2014:306–311
36. van Rooden CJ, Rosendaal FR, Barge RM et al (2003) Central venous catheter related thrombosis in haematology patients and prediction of risk by screening with Doppler-ultrasound. Br J Haematol 123:507–512
37. Bernardi E, Pesavento R, Prandoni P (2006) Upper extremity deep venous thrombosis. Semin Thromb Hemost 32:729–736
38. Bleker SM, van Es N, van Gils L et al (2016) Clinical course of upper extremity deep vein thrombosis in patients with or without cancer: a systematic review. Thromb Res 140(Suppl 1):S81–S88
39. Dentali F, Gianni M, Agnelli G, Ageno W (2008) Association between inherited thrombophilic abnormalities and central venous catheter thrombosis in patients with cancer: a meta-analysis. J Thromb Haemost 6:70–75
40. Bern MM, Lokich JJ, Wallach SR, et al (1990) Very low doses of warfarin can prevent thrombosis in central venous catheters. A randomized prospective trial. Ann Intern Med 112:423–428
41. Monreal M, Alastrue A, Rull M et al (1996) Upper extremity deep venous thrombosis in cancer patients with venous access devices–prophylaxis with a low molecular weight heparin (Fragmin). Thromb Haemost 75:251–253

42. Boraks P, Seale J, Price J et al (1998) Prevention of central venous catheter associated thrombosis using minidose warfarin in patients with haematological malignancies. Br J Haematol 101:483–486
43. Ratcliffe M, Broadfoot C, Davidson M, Kelly KF, Greaves M (1999) Thrombosis, markers of thrombotic risk, indwelling central venous catheters and antithrombotic prophylaxis using low-dose warfarin in subjects with malignant disease. Clin Lab Haematol 21:353–357
44. Heaton DC, Han DY, Inder A (2002) Minidose (1 mg) warfarin as prophylaxis for central vein catheter thrombosis. Intern Med J 32:84–88
45. Mismetti P, Mille D, Laporte S et al (2003) Low-molecular-weight heparin (nadroparin) and very low doses of warfarin in the prevention of upper extremity thrombosis in cancer patients with indwelling long-term central venous catheters: a pilot randomized trial. Haematologica 88:67–73
46. Verso M, Agnelli G, Bertoglio S et al (2005) Enoxaparin for the prevention of venous thromboembolism associated with central vein catheter: a double-blind, placebo-controlled, randomized study in cancer patients. J Clin Oncol 23:4057–4062
47. Couban S, Goodyear M, Burnell M et al (2005) Randomized placebo-controlled study of low-dose warfarin for the prevention of central venous catheter-associated thrombosis in patients with cancer. J Clin Oncol 23:4063–4069
48. Karthaus M, Kretzschmar A, Kroning H et al (2006) Dalteparin for prevention of catheter-related complications in cancer patients with central venous catheters: final results of a double-blind, placebo-controlled phase III trial. Ann Oncol 17:289–296
49. Niers TM, Di Nisio M, Klerk CP, Baarslag HJ, Buller HR, Biemond BJ (2007) Prevention of catheter-related venous thrombosis with nadroparin in patients receiving chemotherapy for hematologic malignancies: a randomized, placebo-controlled study. J Thromb Haemost 5:1878–1882
50. De Cicco M, Matovic M, Balestreri L et al (2009) Early and short-term acenocumarine or dalteparin for the prevention of central vein catheter-related thrombosis in cancer patients: a randomized controlled study based on serial venographies. Ann Oncol 20:1936–1942
51. Young AM, Billingham LJ, Begum G et al (2009) Warfarin thromboprophylaxis in cancer patients with central venous catheters (WARP): an open-label randomised trial. Lancet 373:567–574
52. Lavau-Denes S, Lacroix P, Maubon A et al (2013) Prophylaxis of catheter-related deep vein thrombosis in cancer patients with low-dose warfarin, low molecular weight heparin, or control: a randomized, controlled, phase III study. Cancer Chemother Pharmacol 72:65–73
53. Akl EA, Kamath G, Yosuico V et al (2008) Thromboprophylaxis for patients with cancer and central venous catheters: a systematic review and a meta-analysis. Cancer 112:2483–2492
54. Jimenez-Fonseca P, Carmona-Bayonas A, Calderon C et al (2017) FOTROCAN Delphi consensus statement regarding the prevention and treatment of cancer-associated thrombosis in areas of uncertainty and low quality of evidence. Clin Transl Oncol 19:997–1009
55. Kahn SR, Lim W, Dunn AS et al (2012) Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141:e195S–e226S
56. Debourdeau P, Farge D, Beckers M et al (2013) International clinical practice guidelines for the treatment and prophylaxis of thrombosis associated with central venous catheters in patients with cancer. J Thromb Haemost 11:71–80
57. Schiffer CA, Mangu PB, Wade JC et al (2013) Central venous catheter care for the patient with cancer: American Society of clinical oncology clinical practice guideline. J Clin Oncol 31:1357–1370
58. Streiff MB, Holmstrom B, Ashrani A, et al (2015) Cancer-associated venous thromboembolic disease, version 1.2015. J Natl Compr Canc Netw 13:1079–1095
59. Sousa B, Furlanetto J, Hutka M et al (2015) Central venous access in oncology: ESMO clinical practice guidelines. Ann Oncol 26(Suppl 5):v152–v168

60. Kearon C, Akl EA, Ornelas J et al (2016) Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 149:315–352
61. Lyman GH, Bohlke K, Khorana AA et al (2015) Venous thromboembolism prophylaxis and treatment in patients with cancer: American society of clinical oncology clinical practice guideline update 2014. J Clin Oncol 33:654–656
62. Farge D, Debourdeau P, Beckers M et al (2013) International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. J Thromb Haemost 11:56–70
63. Guyatt G, Gutterman D, Baumann MH et al (2006) Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians task force. Chest 129(1):174–181
64. Guyatt GH, Oxman AD, Kunz R et al (2008) GRADE working group. Rating quality of evidence of and strength of recommendations. BMJ 336:1049–1051
65. Guyatt GH, Oxman AD, Vist GE et al (2008) GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336:924–926
66. Streiff MB, Bockenstedt PL, Cataland SR et al (2013) Venous thromboembolic disease. J Natl Compr Canc Netw. 11(11):1402–1429
67. Grant JD, Stevens SM, Woller SC et al (2012) Diagnosis and management of upper extremity deep-vein thrombosis in adults. Thromb Haemost 108:1097–1108
68. Constans J, Salmi LR, Sevestre-Pietri MA et al (2008) A clinical prediction score for upper extremity deep venous thrombosis. Thromb Haemost 99:202–207
69. Kleinjan A, Di Nisio M, Beyer-Westendorf J et al (2014) Safety and feasibility of a diagnostic algorithm combining clinical probability, d-dimer testing, and ultrasonography for suspected upper extremity deep venous thrombosis: a prospective management study. Ann Intern Med 160:451–457
70. Di Nisio M, Van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW (2010) Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. J Thromb Haemost 8:684–692
71. Bates SM, Jaeschke R, Stevens SM et al (2012) Diagnosis of DVT: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141:e351S–e418S
72. Kovacs MJ, Kahn SR, Rodger M et al (2007) A pilot study of central venous catheter survival in cancer patients using low-molecular-weight heparin (dalteparin) and warfarin without catheter removal for the treatment of upper extremity deep vein thrombosis (The Catheter Study). J Thromb Haemost 5:1650–1653
73. Delluc A, Le Gal G, Scarvelis D, Carrier M (2015) Outcome of central venous catheter associated upper extremity deep vein thrombosis in cancer patients. Thromb Res 135:298–302
74. Francis CW, Kessler CM, Goldhaber SZ et al (2015) Treatment of venous thromboembolism in cancer patients with dalteparin for up to 12 months: the DALTECAN Study. J Thromb Haemost 13:1028–1035
75. Deitcher SR, Kessler CM, Merli G et al (2006) Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period. Clin Appl Thromb Hemost 12:389–396
76. Kahn SR, Springmann V, Schulman S et al (2012) Management and adherence to VTE treatment guidelines in a national prospective cohort study in the Canadian outpatient setting. The recovery study. Thromb Haemost 108:493–498
77. Mahe I, Puget H, Buzzi JC et al (2016) Adherence to treatment guidelines for cancer-associated thrombosis: a French hospital-based cohort study. Support Care Cancer 24:3369–3377

78. Matzdorff A, Schilling H, Ledig B (2015) Treatment of venous thromboembolism in ambulatory cancer patients in Germany: a prospective non-interventional study. Oncol Res Treat 38:174–180
79. Khorana AA, Yannicelli D, McCrae KR et al (2016) Evaluation of US prescription patterns: are treatment guidelines for cancer-associated venous thromboembolism being followed? Thromb Res 145:51–53
80. van der Wall SJ, Klok FA, den Exter PL et al (2017) Continuation of low-molecular-weight heparin treatment for cancer-related venous thromboembolism: a prospective cohort study in daily clinical practice. J Thromb Haemost 15:74–79
81. Carrier M, Cameron C, Delluc A, Castellucci L, Khorana AA, Lee AY (2014) Efficacy and safety of anticoagulant therapy for the treatment of acute cancer-associated thrombosis: a systematic review and meta-analysis. Thromb Res 134:1214–1219
82. van der Hulle T, den Exter PL, Kooiman J, van der Hoeven JJ, Huisman MV, Klok FA (2014) Meta-analysis of the efficacy and safety of new oral anticoagulants in patients with cancer-associated acute venous thromboembolism. J Thromb Haemost 12:1116–1120
83. van Es N, Coppens M, Schulman S, Middeldorp S, Buller HR (2014) Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood 124:1968–1975
84. Larsen TB, Nielsen PB, Skjoth F, Rasmussen LH, Lip GY (2014) Non-vitamin K antagonist oral anticoagulants and the treatment of venous thromboembolism in cancer patients: a semi systematic review and meta-analysis of safety and efficacy outcomes. PLoS ONE 9:e114445
85. Posch F, Konigsbrugge O, Zielinski C, Pabinger I, Ay C (2015) Treatment of venous thromboembolism in patients with cancer: a network meta-analysis comparing efficacy and safety of anticoagulants. Thromb Res 136:582–589
86. Raskob GE, van Es N, Verhamme P, et al (2017) Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med
87. Young A, Marshall A, Thirlwall J, Hill C, Hale D (2017) Anticoagulation therapy in selected cancer patients at risk of recurrence of venous thromboembolism: results of the select-D pilot trial blood. 130(Suppl 1):625a
88. Li A, Garcia DA, Lyman GH, Carrier M (2018) Direct oral anticoagulant (DOAC) versus low-molecular-weight heparin (LMWH) for treatment of cancer associated thrombosis (CAT): a systematic review and meta-analysis. Thromb Res
89. Laube ES, Mantha S, Samedy P, Wills J, Harnicar S, Soff GA (2017) Treatment of central venous catheter-associated deep venous thrombosis in cancer patients with rivaroxaban. Am J Hematol 92:E9–E10
90. Davies GA, Lazo-Langner A, Gandara E et al (2018) A prospective study of Rivaroxaban for central venous catheter associated upper extremity deep vein thrombosis in cancer patients (Catheter 2). Thromb Res 162:88–92
91. Limone BL, Hernandez AV, Michalak D, Bookhart BK, Coleman CI (2013) Timing of recurrent venous thromboembolism early after the index event: a meta-analysis of randomized controlled trials. Thromb Res 132:420–426
92. Owens CA, Bui JT, Knuttinen MG, Gaba RC, Carrillo TC (2010) Pulmonary embolism from upper extremity deep vein thrombosis and the role of superior vena cava filters: a review of the literature. J Vasc Interv Radiol 21:779–787
93. Mewissen MW, Seabrook GR, Meissner MH, Cynamon J, Labropoulos N, Haughton SH (1999) Catheter-directed thrombolysis for lower extremity deep venous thrombosis: report of a national multicenter registry. Radiology 211:39–49
94. Enden T, Haig Y, Klow NE et al (2012) Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. Lancet 379:31–38
95. Haig Y, Enden T, Grotta O et al (2016) Post-thrombotic syndrome after catheter-directed thrombolysis for deep vein thrombosis (CaVenT): 5-year follow-up results of an open-label, randomised controlled trial. Lancet Haematol 3:e64–e71

96. Vik A, Holme PA, Singh K et al (2009) Catheter-directed thrombolysis for treatment of deep venous thrombosis in the upper extremities. Cardiovasc Intervent Radiol 32:980–987
97. Maleux G, Marchal P, Palmers M et al (2010) Catheter-directed thrombolytic therapy for thoracic deep vein thrombosis is safe and effective in selected patients with and without cancer. Eur Radiol 20:2293–2300
98. Schindler J, Bona RD, Chen HH et al (1999) Regional thrombolysis with urokinase for central venous catheter-related thrombosis in patients undergoing high-dose chemotherapy with autologous blood stem cell rescue. Clin Appl Thromb Hemost 5:25–29
99. Baumann Kreuziger L, Cote L, Verhamme P et al (2015) A RIETE registry analysis of recurrent thromboembolism and hemorrhage in patients with catheter-related thrombosis. J Vasc Surg Venous Lymphat Disord 3(243):250.e1
100. Elman EE, Kahn SR (2006) The post-thrombotic syndrome after upper extremity deep venous thrombosis in adults: a systematic review. Thromb Res 117:609–614

Management of Thrombocytopenia in Cancer Patients

9

Jodi V. Mones and Gerald Soff

Contents

9.1 CIT—Definition, Current Treatment with Treatment Complications

Chemotherapy-induced thrombocytopenia (CIT) is a frequent complication of cancer therapy. While there is no standard definition of CIT, we use the term here to specify thrombocytopenia (<100,000/mcL) that persists despite adequate recovery time from prior chemotherapy nadir, in the context of recovery of white cells and red cells. In addition to bleeding, CIT may result in delay or dose reduction in

J. V. Mones (✉) · G. Soff
Hematology Service, Memorial Sloan-Kettering Cancer Center,
1275 York Ave, New York, NY 10065, USA
e-mail: monesj@mskcc.org

G. Soff
e-mail: soffg@mskcc.org

G. Soff (ed.), *Thrombosis and Hemostasis in Cancer*, Cancer Treatment and Research 179, https://doi.org/10.1007/978-3-030-20315-3_9

subsequent cycles of chemotherapy and reduced relative dose intensity (RDI; delivered dose intensity/standard dose intensity) [1–3].

The only current standard management of CIT is support with platelet transfusions. In 2001, an ASCO panel examined the literature regarding platelet transfusions. The purpose of the panel was to determine whether or not a prophylactic transfusion schedule or transfusion upon bleeding was safer and cost-efficient. The ensuing guidelines from this panel propose that for patients with either solid tumors or acute leukemia, a prophylactic approach be followed at platelet nadir of 10,000/mcL or less [4]. Subsequently, in 2015, the AABB reported a similar strategy in accordance with the earlier ASCO panel [5].

In 2017, ASCO published updated guidelines. This update, which incorporated the 2015 AABB recommendations, maintained that patients with CIT be transfused prophylactically at a nadir of 10,000/mcL. This strategy holds true for patients with both hematologic malignancies as well as solid tumor neoplasms. Nonetheless, one of the key changes in the 2017 ASCO update was in adult patients undergoing autologous stem cell transplants. In this patient population, clinicians may decide to wait until the first sign of bleeding to transfuse platelets rather than prophylactically transfuse at a predefined threshold [6].

Stanworth and colleagues, in the Trial of Prophylactic Platelets study (TOPPS) conducted a randomized trial comparing different transfusion strategies in patients with acute leukemia. This study randomized 600 patients with acute leukemia to either receive prophylactic platelet transfusions once platelet counts reached below 10,000/mcL or observation. In the observation group, the use of platelet transfusions was significantly lower; however, the risk of bleeding (using the WHO scale) was higher. In the prophylaxis, cohort bleeding occurred in 43% of patients, whereas in the no-prophylaxis group, 50% of patients bled ($P = 0.06$, CI 1.7–15.2) [7].

The use of prophylactic transfusions, while decreasing the morbidity and mortality associated with hemorrhage, does have risks and complications. Platelets are stored at room temperature and thus have a shelf-life of only five days. The ability to maintain an adequate supply of platelet products requires significant resources, especially in a cancer center where CIT is commonplace. Putting cost aside, there are other risks associated with transfusion of platelets. Bacterial contamination of platelets leading to infection or even sepsis is an uncommon but a real concern due to storage at room temperature [8]. Patients can also develop allergic and/or febrile reactions to platelet products. Finally, with frequent transfusions, patients run the risk of alloimmunization, becoming refractory to ongoing platelet transfusion support.

9.2 Causes of Thrombocytopenia in Cancer Patients

Chemotherapy is the major cause of thrombocytopenia in cancer patients. However, there are other causes of thrombocytopenia in cancer patients as well. Myelophthisis (marrow infiltration), infection, graft versus host disease, other drugs, and liver dysfunction may also contribute to thrombocytopenia [9]. The liver is the

primary source of thrombopoietin production [10]. Tumor invasion, underlying liver disorders, and chemotherapy, together or independently, can have ill-effects on the liver resulting in a decrease of thrombopoietin production. Both solid and hematologic malignances can invade the bone marrow resulting in decreased platelet production by limiting megakaryocyte growth and/or maturation. Hepatic sinusoidal obstructive syndrome as well as splenic enlargement which have been associated with adjuvant FOLFOX can contribute to resultant thrombocytopenia often seen in patients with colorectal cancer [11]. Mitomycin-C, gemcitabine, and oxaliplatin among others can cause a micro-angiopathic hemolytic anemia (MAHA). Hemolysis from gemcitabine is typically dose-dependent, whereas oxaliplatin can have an idiosyncratic effect [12, 13]. Fludarabine is well known in some instances to cause an immune-mediated thrombocytopenia [14].

9.3 Complications of CIT: Bleeding, Dose Reductions, Alloimmunization

Chemotherapy-induced thrombocytopenia, regardless of the cause, carries with it several complications. In addition to the risk of bleeding, reduction in RDI is common and may impact cancer control. One retrospective study of 609 patients with both solid tumors and lymphoma illustrated the risk of bleeding with CIT, defined here as <50,000/mcL. Patients were stratified according to tumor type. Overall bleeding occurred in 9% of patients, and most bleeds were minor per the WHO definition of grade 1 and 2 bleeding. In 8% of patients who developed CIT (<50,000/mcL), there was a dose delay of at least seven days until the next treatment cycle and 17% had at least a 20% reduction in their subsequent doses. Among patients who did have bleeding associated with CIT 22% had dose delays or reductions. Of particular interest was that in patients whose treatment was complicated by a major bleeding episode survived on average 5.9 months versus 15 months in patients without major bleeding ($P < 0.0001$). This difference was limited to the patient with disseminated disease [2].

What role does the reduction of chemotherapy dosing play? Nakayama and colleagues evaluated RDI in patients with metastatic colorectal cancer [15]. The overall response rates (ORR), disease control rates (DCR), and progression-free survival (PFS) were shorter in patients with lower RDI. Patients treated with fluorouracil and irinotecan (FOLFIRI) receiving full RDI ($\geq 80\%$) mean progression-free survival were 9.9 months, compared with 5.6 months in patients requiring reduced RDI ($P < 0.01$). There also was a marked improved overall survival (OS) with full RDI versus reduced RDI (26.7 months vs. 12.9 months, $P = 0.01$). For patients treated with fluorouracil and oxaliplatin (mFOLFOX6), there was a trend toward improved PFS as well with full versus reduced RDI (8.5 months vs. 6.2 months, $P = 0.06$), but no impact on OS [15]. While there are a number of factors that may impact RDI, CIT is a major cause, and this supports the need to develop better strategies for the treatment of CIT.

9.4 Background of Alternate Treatments to Transfusions

At present, the most common way for clinicians to manage CIT is with dose delays, dose reductions, or platelet transfusions. Quantifying the frequency and severity of these strategies is difficult given the variation among practitioners. For example, an investigation of the consequences and treatment of CIT in two large clinical trials using FOLFOX4 and FOLFIRI was presented at ESMO in 2017. All patients had metastatic colorectal cancer either to the liver or another site. 37% of patients on FOLFOX4 and 4% on FOLFIRI experienced CIT during a median of one-year follow-up. In the FOLFOX4 cohort, dose delay, dose change, or both occurred at 81, 63, and 59%, respectively. For FOLFIRI, the numbers were lower at 72, 49, and 47% for dose delay, dose change, or both, respectively [16].

In addition to dose delay/reduction, practitioners often use platelet transfusions as a way to treat CIT. However, the duration of the effect of platelet transfusions is short and cannot prevent the severity of subsequent nadir. Further, frequent platelet transfusions are fraught with complications. Because of these difficulties, alternative CIT treatment strategies have been sought. One early attempt was the development of recombinant human IL-11 (rhIL-11). rhIL-11 was studied in a randomized, placebo-controlled study comparing two doses of rhIL-11 to placebo [17]. Patients could have had either solid malignancies or non-Hodgkin's lymphoma. Patients who received rhIL-11 at 50 mcg/kg did have a significant ($P < 0.05$) decrease in platelet transfusion requirements compared to placebo [17]. However, it should be noted that platelet threshold at the time was <20,000/mcL, higher than the current recommendations. Also, the side-effect profile of rhIL-11 was problematic, including edema, headaches, tachycardia, and palpitations. Similar results were published the following year in patients receiving dose-intense cyclophosphamide with doxorubicin for breast cancer [17]. Patients were given rhIL-11 or placebo for ten or seventeen days after their first two chemotherapy cycles. Results showed a significant decrease ($P = 0.04$) in platelet transfusion requirement compared to placebo. Adverse events were related to fluid retention and included dyspnea, edema, and pleural effusions [17]. The FDA approved rhIL-11, however, due to the adverse side-effect profile use of the medication did not enter standard practice.

9.5 Development of TPO Agents

In 1994, several groups reported the cloning of a megakaryocyte growth factor that was a ligand for the c-Mpl receptor [18, 19]. Subsequently, two recombinant thrombopoietin proteins were developed: recombinant human thrombopoietin (rhTPO) and pegylated human recombinant megakaryocyte growth and development factor (PEG-rHuMGDF) [20]. Unfortunately, clinical development of these first-generation TPO growth factors was stopped after volunteers developed auto-antibodies to endogenous TPO after exposure to PEG-rHuMDGF [21]. Since then, several second-generation thrombopoietin growth factors have been

developed. These are TPO "mimetic" agents: both peptide and non-peptide forms [20]. Two, in particular, romiplostim and eltrombopag, have been approved and made their way into clinic use in a variety of settings, particularly immune thrombocytopenia.

More recently, an additional oral TPO-receptor agonist, Avatrombopag, has been shown to be effective in patients with chronic ITP [22]. Several abstracts at the 2017 ASH meeting showed the efficacy of avatrombopag in liver disease as well as chronic ITP [23–25], and in 2018, it was approved for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure.

9.6 Recent Studies of TPO Agents in CIT

Currently, no TPO growth factor has been approved for CIT. Both eltrombopag and romiplostim are currently under exploration for this indication. Investigation of eltrombopag began in early 2010 in patients receiving chemotherapy for solid tumors [26, 27]. In 2016, a small study was published evaluating eltrombopag 25 mg twice weekly in patients receiving cytotoxic chemotherapy. Indications for chemotherapy varied and included both solid tumors and non-Hodgkin's lymphoma (DLBCL). Endpoints were to avoid platelet nadir <50,000/mcL, avoid platelet transfusions, prevent bleeding, and reduce the number of chemotherapy dose delay/reductions. Eltrombopag was begun once platelet counts fell below 80,000/mcL and was continued throughout treatment. Twenty-two patients were enrolled; twenty-one responded to the planned dose. There were no treatment-related toxicities. The primary endpoints were met with a mean platelet nadir of 60,000/mcL [28].

Recently, a phase II placebo-controlled study was published looking at the use of eltrombopag in solid tumor patients receiving gemcitabine-based chemotherapy. Patients were randomized in 2:1 fashion either to eltrombopag 100 mg daily or placebo starting on day −5 to −1 and then again on days 2–6 of each cycle. In this study, patients could be either treatment naïve or on a subsequent line of therapy. The eligible platelet counts were as follows: (1) platelets < 150,000/mcL on days −8 to −5 prior to starting the first cycle; (2) platelets < 150,000/mcL on day 1; (3) platelets < 100,000/mcL on day 8 of the preceding cycle in patients who have already received treatment. Also of note is that patients were excluded if they had a history of either arterial or venous thrombosis within the preceding 6 months. The primary endpoint was the average day 1 platelet count across six cycles [29].

Seventy-five patients were enrolled. 64% of the eltrombopag-treated patients withdrew from the study for both adverse events as well as at the investigator's discretion. Ultimately, 11 patients on gemcitabine monotherapy arm and eight in the combination chemotherapy arm completed the study. Patients in the eltrombopag groups had fewer dose delays, dose reductions, or missed doses (combination 77 vs. 91%; monotherapy 62 vs. 83%). The most common adverse event in the

eltrombopag arms was hepatobiliary toxicity. While an encouraging trend, the small numbers and a high number of patients withdrawing from the study limits conclusions [29].

Chawla et al. looked at eltrombopag in patients with soft tissue sarcomas receiving Ifosfamide/doxorubicin (AI) chemotherapy. Historically, this regimen is associated with a 63% incidence of grade 3/4 thrombocytopenia [30]. This was a phase I dose escalation investigation. Patients were started on eltrombopag 75 mg either 5 days prior (−5) to the start of their second cycle of AI with continuation for 5 days after (+5) or days 5–14 after AI. Escalation was safely executed up to the 150 mg dose without significant adverse events. Unfortunately, due to slow recruitment, the study was closed early so definite conclusions are limited. However, the use of eltrombopag with AI in soft tissue sarcomas appears to be safe and well tolerated [31].

Studies looking at the use of romiplostim for CIT are promising. A cohort of 20 patients with solid tumors and dose-limiting CIT, treated with romiplostim, was published in Supportive Care in Cancer [32]. Weekly dosing of romiplostim was started at 1–2 mcg/kg and titrated up until recovery (>100,000/mcL). All patients had an improvement in their platelet counts and 19 of the 20 corrected their platelet counts to >100,000/mcL within 2 weeks for romiplostim treatment. Romiplostim was well tolerated with very few adverse events. Three patients developed deep vein thrombosis, consistent with what is expected of patients in this population [33].

To further investigate the efficacy and safety of romiplostim for CIT, our group at Memorial Sloan Kettering began a Quality Assessment/Improvement Initiative. The purpose of this project was to analyze the patients at MSKCC who received romiplostim off-label and off-study for CIT and evaluate the efficacy and rates of

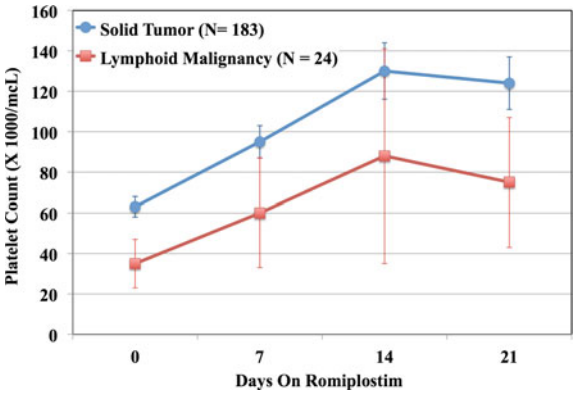

Fig. 9.1 Platelet Count Recovery After Initiation of Romiplostim. 183 patients with solid tumor, and 24 patients with lymphoid malignancies (lymphoma or myeloma) received romiplostim. Mean platelet counts at least doubled by day 14 in both groups, beyond which the platelet counts reflected the competing effects of maintenance romiplostim support and platelet suppression by chemotherapy. Platelet counts are mean +/- 95% confidence interval

thrombosis. We identified 239 patients from 2010 to 2017. The majority of the patients had solid tumors. However, the analysis did include patients with myeloma as well as lymphoid malignancies. The mean platelet counts doubled by day 14 in subjects with both solid and hematologic malignancies (Fig. 9.1) [34].

The safety analysis of the Quality Assessment Initiative focused on assessing the risk of venous thrombosis in patients receiving romiplostim. There were a total of 15 venous thrombotic events. This translates into 11.6% venous thrombotic events per patient-year; well within the expected rate of VTE in cancer patients [33].

A recent retrospective case series by Al-Samkari and colleagues also suggests that the use of romiplostim for chemotherapy-induced thrombocytopenia (CIT) can reduce dose reductions/delays in chemotherapy [35]. In this retrospective case series, romiplostim treatment of CIT led to a significant reduction in both chemotherapy dose delays and dose reductions. The median dose of romiplostim was 3 mcg/kg (range 1–10). Also encouraging was that there were no thrombotic events observed [35]. Whether or not such improvements in chemotherapy delivery will translate into improved overall survival is yet to be determined. As mentioned earlier, past studies suggest preservation of chemotherapy relative dose intensity results in better outcomes [15, 36]. However, more data and randomized prospective studies are needed to establish such conclusions.

A prospective, randomized study of romiplostim treatment for CIT in solid tumor patients has been completed and was presented at the American Society of Hematology in 2017 [37]. This was a phase II open-label study in solid tumor patients with a platelet count of <100,000/mcL. Initially, patients were randomized in a 2:1 ratio to romiplostim or observation. However, after an interim analysis revealed a significant benefit of romiplostim ($P = 0.0002$), with IRB approval, the observation arm was discontinued. Primary endpoint was correction of platelet counts to >100,000/mcL within 3 weeks [37].

At the time of presentation, 40 patients were enrolled of which the majority had gastrointestinal malignancies. Thirty-two received romiplostim upfront. 84% met the primary endpoint reaching a platelet count of >100,000/mcL within three weeks. Romiplostim treatment was superior to observation control in correcting thrombocytopenia within 3 weeks (84% vs. 12.5%, $p = 0.0002$), and allowing for the resumption of chemotherapy. The mean effective dose was 2.5 mcg/kg (range 1.8–4.1). Most importantly, 25 patients were able to resume their chemotherapy after correction of their platelet counts. Only one patient had a recurrence of their CIT [37].

The secondary safety endpoints of the study were also favorable. There was no evidence of myelofibrosis in any of the patients in the study. Four patients (12.5%) had venous thrombotic events (two with pulmonary emboli and two with deep vein thrombosis), which is within the expected range for this high-risk population [33]. The final report of this study has been submitted for publication. Romiplostim treatment of CIT appears to be safe in cancer patients when used to treat CIT, with no evidence of increased thrombotic risk [34, 35, 37]. Cancer itself, as well as ongoing chemotherapy, predispose to thrombosis. However, in this new case series

Table 9.1 Analysis from phase II study of romiplostim versus observation control for chemotherapy-induced thrombocytopenia [37]

A: Primary endpoint (ITT): Interim analysis			
	≥100,000/mcL within 3 weeks	Failed to correct within 3 weeks	Total
Romiplostim (randomized phase)	14 (93%)**	1	15
Observation	1 (12.5%)**	7	8
$^{**}P = 0.0002$ by Fisher's exact test			
B: Primary endpoint: Romiplostim single-arm phase, and all romiplostim-treated patients			
	≥100,000/mcL within 3 weeks	Failed to correct within 3 weeks	Total
Romiplostim (single-arm phase)	30 (81%)	7	37
Romiplostim (all patients)	44 (85%)	8	52

Table 9.2 Treatment of patients with solid tumor or lymphoid malignancies (lymphoma or myeloma) with romiplostim resulted in a greater than doubling of mean platelet counts by day 14. From [34]

	Day 0	Day 7	Day 14	Day 21
Solid tumor (n = 183)	63 (±5)	95 (±8)	130 (±14)	124 (±13)
Lymphoid malignancies[a] (n = 24)	35 (±12)	60 (±27)	88 (±53)	75 (±32)

Platelet count x 10^9/L; ± margin is 95% confidence interval
[a]Lymphoma/myeloma: The analysis of hematologic malignancies does not include leukemia, MDS, or BMT patients

as well as past studies, the rate of thrombosis in patients treated with romiplostim does not exceed the anticipated rate (Table 9.1).

In summary, the use of TPO-stimulating agents to treat CIT is promising and may provide a way for patients to receive potentially life-saving chemotherapy. Both eltrombopag and romiplostim have been studied and appear effective. Eltrombopag has the advantage of oral administration. However, dietary and medication interactions as well as a box warning for risk of hepatotoxicity limit use [38]. It is also worth noting that in the recent clinical trial of eltrombopag for CIT, almost two-thirds of the patients were withdrawn from the study [29]. Romiplostim, administered as a subcutaneous injection, has minimal adverse events and drug-drug interactions [39]. The efficacy and safety of romiplostim in CIT have been demonstrated in several case series, as well as one recent randomized phase II trial.

It is yet to be determined if successful treatment of CIT with a TPO-receptor agonist will translate into improved cancer outcomes. Whether or not use of TPO agents to lessen dose reductions and dose delays of therapy will translate into

improved overall survival or progression free survival is ultimately what matters most to our patients (Table 9.2).

9.7 Management of Anticoagulation in the Setting of CIT

Clinicians caring for cancer patients are often faced with the dilemma of managing anticoagulation in the setting of thrombocytopenia. Although there was little data to base guidelines, in 2009, Lee suggested a reasonable strategy of anticoagulation dose modification in the setting of chemotherapy-induced thrombocytopenia [40]. Based on the article, in 2010, Memorial Sloan Kettering Cancer Center the following guideline: Administer full-dose enoxaparin for a platelet count >50,000/mcL, half-dose enoxaparin for a platelet count between 25,000 and 50,000/mcL, and no anticoagulation in patients whose platelet count is <25,000/mcL.

Subsequently, this approach was validated in a Quality Assessment Initiative (QAI), the results from which were published in 2017 [41]. At MSKCC, 99 patients (140 episodes) experienced thrombocytopenia (<50,000/mcL) lasting >7 days while on therapeutic enoxaparin prior to their platelet nadir. The key findings from this QAI were that there were no episodes of major bleeds among the patients who had their anticoagulation adjusted per the MSKCC guidelines. Equally important was that there were no recurrent VTEs during the 140 episodes of thrombocytopenia and dose-reduced enoxaparin. This provides assurance for clinicians regarding the safety and efficacy of reduced dose anticoagulation in patients with thrombocytopenia [41, 42].

The National Comprehensive Cancer Network (NCCN) has now incorporated this dosing strategy into the current Cancer-Associated Venous Thromboembolic Disease guidelines [43]. The updated International Society of Thrombosis and Hemostasis (ISTH) guidelines regarding management of anticoagulation among patients with thrombocytopenia due to cancer or cancer treatment are similar [44]. However, the ISTH recommends full-dose anticoagulation with platelet transfusions to a goal of >40,000/mcL in cancer patients with an acute cancer-associated thrombus and a high risk of thrombus progression [44, 45].

References

1. Denduluri N, Patt DA, Wang Y, Bhor M, Li X, Favret AM et al (2015) Dose delays, dose reductions, and relative dose intensity in patients with cancer who received adjuvant or neoadjuvant chemotherapy in community oncology practices. J Natl Compr Canc Netw 13 (11):1383–1393
2. Elting LS, Rubenstein EB, Martin CG, Kurtin D, Rodriguez S, Laiho E et al (2001) Incidence, cost, and outcomes of bleeding and chemotherapy dose modification among solid tumor patients with chemotherapy-induced thrombocytopenia. J Clin Oncol 19(4):1137–1146

3. Lyman GH, Dale DC, Crawford J (2003) Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. J Clin Oncol 21(24):4524–4531
4. Schiffer CA, Anderson KC, Bennett CL, Bernstein S, Elting LS, Goldsmith M et al (2001) Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 19(5):1519–1538
5. Kaufman RM, Djulbegovic B, Gernsheimer T, Kleinman S, Tinmouth AT, Capocelli KE et al (2015) Platelet transfusion: a clinical practice guideline from the AABB. Ann Intern Med 162 (3):205–213
6. Schiffer CA, Bohlke K, Delaney M, Hume H, Magdalinski AJ, McCullough JJ et al (2018) Platelet transfusion for patients with cancer: American Society of Clinical Oncology Clinical practice guideline update. J Clin Oncol 36(3):283–299
7. Stanworth SJ, Estcourt LJ, Powter G, Kahan BC, Dyer C, Choo L et al (2013) A no-prophylaxis platelet-transfusion strategy for hematologic cancers. N Engl J Med 368 (19):1771–1780
8. Stramer SL (2007) Current risks of transfusion-transmitted agents: a review. Arch Pathol Lab Med 131(5):702–707
9. Mantha S, Miao Y, Wills J, Parameswaran R, Soff GA (2017) Enoxaparin dose reduction for thrombocytopenia in patients with cancer: a quality assessment study. J Thromb Thrombolysis 43(4):514–518
10. de Sauvage FJ, Hass PE, Spencer SD, Malloy BE, Gurney AL, Spencer SA et al (1994) Stimulation of megakaryocytopoiesis and thrombopoiesis by the c-Mpl ligand. Nature 369 (6481):533–538
11. Politano S, Pathak P, Hoff PM, Charnsangavej C, Overman MJ, Loyer E et al (2008) The use of 5-fluorouracil and oxaliplatin (FOLFOX) for colorectal cancer is associated with the development of splenomegaly and thrombocytopenia. J Clin Oncol 26(15_suppl):4102
12. Al-Nouri ZL, Reese JA, Terrell DR, Vesely SK, George JN (2015) Drug-induced thrombotic microangiopathy: a systematic review of published reports. Blood 125(4):616–618
13. Glezerman I, Kris MG, Miller V, Seshan S, Flombaum CD (2009) Gemcitabine nephrotoxicity and hemolytic uremic syndrome: report of 29 cases from a single institution. Clin Nephrol 71(2):130–139
14. Hegde UP, Wilson WH, White T, Cheson BD (2002) Rituximab treatment of refractory fludarabine-associated immune thrombocytopenia in chronic lymphocytic leukemia. Blood 100(6):2260–2262
15. Nakayama G, Tanaka C, Uehara K, Mashita N, Hayashi N, Kobayashi D et al (2014) The impact of dose/time modification in irinotecan- and oxaliplatin-based chemotherapies on outcomes in metastatic colorectal cancer. Cancer Chemother Pharmacol 73(4):847–855
16. Cetin K, Toler A, Eisen M, Soff GA (2017) Chemotherapy-induced thrombocytopenia (CIT) in metastatic colorectal cancer (mCRC) patients. Ann Oncol 28(suppl. 5):596
17. Tepler I, Elias L, Smith JW 2nd, Hussein M, Rosen G, Chang AY et al (1996) A randomized placebo-controlled trial of recombinant human interleukin-11 in cancer patients with severe thrombocytopenia due to chemotherapy. Blood 87(9):3607–3614
18. Bartley TD, Bogenberger J, Hunt P, Li YS, Lu HS, Martin F et al (1994) Identification and cloning of a megakaryocyte growth and development factor that is a ligand for the cytokine receptor Mpl. Cell 77(7):1117–1124
19. Lok S, Kaushansky K, Holly RD, Kuijper JL, Lofton-Day CE, Oort PJ et al (1994) Cloning and expression of murine thrombopoietin cDNA and stimulation of platelet production in vivo. Nature 369(6481):565–568
20. Kuter DJ (2007) New thrombopoietic growth factors. Blood 109(11):4607–4616
21. Basser RL, O'Flaherty E, Green M, Edmonds M, Nichol J, Menchaca DM et al (2002) Development of pancytopenia with neutralizing antibodies to thrombopoietin after multicycle

chemotherapy supported by megakaryocyte growth and development factor. Blood 99 (7):2599–2602
22. Bussel JB, Kuter DJ, Aledort LM, Kessler CM, Cuker A, Pendergrass KB et al (2014) A randomized trial of avatrombopag, an investigational thrombopoietin-receptor agonist, in persistent and chronic immune thrombocytopenia. Blood 123(25):3887–3894
23. Frelinger AL, Smolensky Koganov E, Forde EE, Carmichael SL, Michelson AD (2017) Avatrombopag, a novel thrombopoietin receptor agonist, increases platelet counts without increasing platelet activation in patients with thrombocytopenia due to chronic liver disease. Blood 130(Suppl 1):290
24. Jurczak W, Chojnowski K, Mayer J, Krawczyk K, Bibbiani F (2017) Avatrombopag, a novel oral thrombopoietin receptor agonist, demonstrates superiority to placebo for the treatment of chronic immune thrombocytopenic purpura in a phase 3, multicenter, randomized, double-blind, placebo-controlled trial. Blood 130(Suppl 1):17
25. Terrault N, Kuter DJ, Izumi N, Kayali Z, Mitrut P, Tak WY et al (2017) Superiority of Avatrombopag to placebo in increasing platelet counts in patients with chronic liver disease-associated thrombocytopenia undergoing scheduled procedures: results from 2, phase 3 randomized studies. Blood 130(Suppl 1):18
26. Hayes S, Mudd PN Jr, Ouellet D, Johnson BM, Williams D, Gibiansky E (2013) Population PK/PD modeling of eltrombopag in subjects with advanced solid tumors with chemotherapy-induced thrombocytopenia. Cancer Chemother Pharmacol 71(6):1507–1520
27. Kellum A, Jagiello-Gruszfeld A, Bondarenko IN, Patwardhan R, Messam C, Mostafa Kamel Y (2010) A randomized, double-blind, placebo-controlled, dose ranging study to assess the efficacy and safety of eltrombopag in patients receiving carboplatin/paclitaxel for advanced solid tumors. Curr Med Res Opin 26(10):2339–2346
28. Iuliano F, Iuliano E, Perricelli A, Santoro MA, Pomillo A, Luci M et al (2016) Low doses of eltrombopag are safe and effective in the prophylaxis of the chemotherapy-induced thrombocytopenia (CIT). Blood 128(22):4926
29. Winer ES, Safran H, Karaszewska B, Bauer S, Khan D, Doerfel S et al (2017) Eltrombopag for thrombocytopenia in patients with advanced solid tumors receiving gemcitabine-based chemotherapy: a randomized, placebo-controlled phase 2 study. Int J Hematol 106(6):765–776
30. Worden FP, Taylor JM, Biermann JS, Sondak VK, Leu KM, Chugh R et al (2005) Randomized phase II evaluation of 6 g/m^2 of ifosfamide plus doxorubicin and granulocyte colony-stimulating factor (G-CSF) compared with 12 g/m^2 of ifosfamide plus doxorubicin and G-CSF in the treatment of poor-prognosis soft tissue sarcoma. J Clin Oncol 23(1):105–112
31. Chawla SP, Staddon A, Hendifar A, Messam CA, Patwardhan R, Kamel YM (2013) Results of a phase I dose escalation study of eltrombopag in patients with advanced soft tissue sarcoma receiving doxorubicin and ifosfamide. BMC Cancer 13:121
32. Parameswaran R, Lunning M, Mantha S, Devlin S, Hamilton A, Schwartz G et al (2014) Romiplostim for management of chemotherapy-induced thrombocytopenia. Support Care Cancer 22(5):1217–1222
33. Khorana AA, Dalal M, Lin J, Connolly GC (2013) Incidence and predictors of venous thromboembolism (VTE) among ambulatory high-risk cancer patients undergoing chemotherapy in the United States. Cancer 119(3):648–655
34. Li VJ, Miao Y, Wilkins C, Soff GA (2017) Efficacy and thrombotic adverse events of romiplostim use in patients with thrombocytopenia related to underlying malignancies. Blood 130(Suppl 1):2324
35. Al-Samkari H, Marshall AL, Goodarzi K, Kuter DJ (2018) The use of romiplostim in treating chemotherapy-induced thrombocytopenia in patients with solid tumors. Haematologica 103 (4):e169–e172

36. Moskowitz CH, Hamlin PA, Gabrilove J, Bertino JR, Portlock CS, Straus DJ et al (2007) Maintaining the dose intensity of ICE chemotherapy with a thrombopoietic agent, PEG-rHuMGDF, may confer a survival advantage in relapsed and refractory aggressive non-Hodgkin lymphoma. Ann Oncol 18(11):1842–1850
37. Soff GA, Miao Y, Devlin SM, Mantha S, Mones JV, Li VJ et al (2017) Romiplostim for chemotherapy-induced thrombocytopenia (CIT). Results of a phase 2 trial. Blood 130(Suppl 1):289
38. Information PeP. https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/promacta.pdf
39. Information NrP. https://pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/nplate/nplate_pi_hcp_english.pdf
40. Mantha S, Miao Y, Wills J, Parameswaran R, Soff GA (2017) Enoxaparin dose reduction for thrombocytopenia in patients with cancer: a quality assessment study. J Thromb Thrombolysis 43:514–518
41. Lee Agnes YY (2009) Anticoagulation in the treatment of established venous thromboembolism in patients with Cancer. J Clinic Oncol 27(29):4895–4901. https://doi.org/10.1200/JCO.2009.22.3958
42. Mantha S, Gupta D, Salmane C, Khaddr M, Soff GA, Steingart R (2018) Anticoagulation in the patient with cancer. In: Lau JF, Barnes GD, Streiff MB (eds) Anticoagulation therapy. Springer International Publishing, Cham, pp 425–440
43. NCCN Guidelines Version 1.2019 Cancer-Associated Venous Thromboembolic Disease February 28, 2019. https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf
44. Samuelson Bannow BT, Lee A, Khorana AA, Zwicker JI, Noble S, Ay C, Carrier M (2018) Management of cancer-associated thrombosis in patients with thrombocytopenia: guidance from the SSC of the ISTH. J Thrombosis Haemost 16:1246–1249
45. Samuelson Bannow BR, Lee AYY, Khorana AA, Zwicker JI, Noble S, Ay C et al (2018) Management of anticoagulation for cancer-associated thrombosis in patients with thrombocytopenia: a systematic review. Res Pract Thrombosis Haemost 2(4):664–669

Microangiopathy in Cancer: Causes, Consequences, and Management

10

Mari R. Thomas and Marie Scully

Contents

Thrombotic microangiopathy (TMA) is a syndrome defined clinically by fragmentation haemolysis/microangiopathic haemolytic anaemia (MAHA) and thrombocytopenia (MAHAT). There is red cell fragmentation on the blood film and a reduced platelet count. Additional evidence of haemolysis includes elevated lactate dehydrogenase (LDH), reticulocytosis, low/absent haptoglobin, and often raised unconjugated bilirubin. Clinical symptoms and signs can be variable and will depend in part on the underlying diagnosis [20]. Histologically, there is systemic thrombus formation affecting small or larger vessels, with thrombi varying in their constituents depending on the underlying cause of the TMA.

M. R. Thomas (✉) · M. Scully
University College London Hospitals, London, UK
e-mail: mari.thomas@ucl.ac.uk

M. Scully
e-mail: m.scully@ucl.ac.uk

G. Soff (ed.), *Thrombosis and Hemostasis in Cancer*, Cancer Treatment and Research 179, https://doi.org/10.1007/978-3-030-20315-3_10

10.1 Differential Diagnosis of TMA

TMA in cancer patients may be directly related to the underlying malignancy (either the initial presentation or with progressive disease), to treatment of the cancer, or it may be a separate incidental diagnosis. It is vital to differentiate thrombotic thrombocytopenic purpura (TTP) and atypical haemolytic uraemic syndrome (aHUS) in patients presenting with MAHAT as quickly as possible, as they have different treatment strategies, and prompt initiation of treatment has a critical impact on the outcome.

TTP is caused by severe ADAMTS13 deficiency, leading to persistence of highly haemostatically reactive ultra-large VWF multimers resulting in VWF–platelet microthrombi formation. Presenting features are diverse and related to organ dysfunction, with neurological and cardiac involvement being common. The majority of TTP cases are immune-mediated (iTTP), although a congenital form of the condition may be seen due to biallelic mutations in the *ADAMTS13* gene.

Shiga toxin-induced HUS (**STEC-HUS**) is caused by enteric infection with Shiga toxin-secreting bacteria such as *E. coli* 0157. It is more frequently seen in children with a prodrome of abdominal pain and classically bloody diarrhoea. Complement-mediated HUS (**CM-HUS**, also described as atypical HUS, aHUS) is an extremely rare but increasing appreciated cause of a TMA which is important to recognise because of its response to complement inhibition.

Cancer TMA: TMA may be the presenting feature of an underlying cancer or seen in end-stage metastatic disease. Cancer can cause MAHAT by systemic microvascular metastases, as microvascular obstruction by tumour cells causes red cell fragmentation and platelet consumption in the tumour emboli. MAHAT can also be due to extensive bone marrow involvement with cancer or secondary necrosis [14]. The majority of cases are solid tumours, but haematological cancers such as lymphoma make up approximately 8% of all cases [10]. Gastric, lung, breast, and prostate cancers, primarily adenocarcinoma, are the most likely diagnoses. Cancer-associated TMA is more likely to have bone pain at presentation than TTP and have an inadequate response to PEX [3].

Respiratory symptoms (which are rare in TTP) have been associated with over 70% of cases of cancer-associated TMA in one series [2] with an increase in disseminated intravascular coagulation (DIC). Abnormal liver function tests and moderate to severe renal impairment are also more common in cancer-associated TMA [14]. Review of the blood film and an early bone marrow biopsy may help expedite the underlying cancer diagnosis [8].

Disseminated intravascular coagulation (DIC) is a clinicopathological syndrome that can be precipitated in oncology patients by sepsis or driven by the cancer itself. Certain tumours are more prone to provoking DIC, particularly adenocarcinomas of the gastrointestinal tract (frequently signet ring cell type), pancreas, lung, breast, or prostate. Mucinous tumours can secrete enzymes capable of activating coagulation factor X [14]. DIC occurs in most patients with acute

promyelocytic leukaemia, caused by the release of procoagulants by abnormal promyelocytes [21].

Thrombocytopenia is the first and most sensitive sign of DIC present in >90% of cases, and 50% of cases have platelet levels $<50 \times 10^9$/L. The falling platelet count is associated with increased thrombin formation and fibrinolytic activity, resulting in raised D-dimers. There is variability in the coagulation screen (PT (prothrombin time) and/or APTT (activated partial thromboplastin time)), which is prolonged in 60–70% cases, but can be normal or indeed shortened. Fibrinogen may be reduced but is not commonly below the normal laboratory range unless very severe DIC. It is the sequential changes in these laboratory parameters that is more helpful in confirming a diagnosis of DIC. Use of scoring systems improves diagnostic accuracy, with the ISTH scoring system for DIC being >90% sensitive and specific, and associated with increased mortality [11].

Drugs and TMA are a rare but important cause of TMA and may cause TMA either by dose-dependent toxicity or immune-mediated reaction after the development of drug-dependent antibodies [1]. In the majority of cases, the clinical presentation involves primarily a renal component in conjunction with MAHAT. A drug-dependent antibody should be considered if symptoms are sudden and recurrent with repeated administration of a drug. However, if there is slow progressive kidney injury with a TMA, then dose-dependent toxicity may be more likely [14].

Chemotherapeutic agents which have been associated with TMA include gemcitabine, which causes dose-dependent, predominantly renal, endothelial damage, and oxaliplatin where drug-dependent antibodies against red cells and platelets occur. Proteasome inhibitor-associated thrombotic microangiopathy is increasingly recognised. One recent case series describes 11 patients who developed TMA while being treated with bortezomib or carfilzomib at a median of 21 days (5 days–17 months) after starting the drug in myeloma therapy. Nine had a resolution of TMA after the withdrawal of proteasome inhibitor (PI); two had stabilisation of laboratory values but persistent haemolysis despite medication withdrawal, and one patient had a recurrence of TMA with rechallenge of PI [26]. A list of drugs which have been associated with TMA with potential mechanisms and therapy is given in Table 10.1.

Transplant-associated TMA (TA-TMA) may affect either solid organ or HSCT patients. TA-TMA remains a difficult complication to address due to its high mortality rate, lack of standard diagnostic criteria, and limited therapeutic options [9]. The underlying pathology is complex with multiple contributing factors that converge on a final pathway involving widespread endothelial injury and complement activation. Risk factors leading to endothelial damage include underlying conditioning therapy, HLA-mismatched transplants, and calcineurin inhibitors used to prevent rejection. It is important to consider additional underlying infections such as adenovirus, with nearly 50% of patients at post-mortem having evidence of viraemia. Mortality is significant, and poor prognostic factors include proteinuria, raised LDH, and hypertension [5].

Table 10.1 Drugs associated with thrombotic microangiopathy

Drug	Possible pathogenesis and treatment
Ticlopidine	Specific to ticlopidine, and not other thienopyridines Anti-ADAMTS13 antibodies present Respond to PEX
Gemcitabine	Dose-dependent endothelial damage, predominantly glomerular arterioles/capillaries May respond to complement inhibition
Platinum-based drugs, e.g. oxaliplatin	Oxaliplatin-dependent antibodies against erythrocytes and platelets
Mitomycin C	Dose-dependent toxicity, cumulative renal damage with microthrombi in glomerular capillaries and arterioles
VEGF inhibitors, e.g. bevacizumab and aflibercept	Dose-dependent toxicity Microthrombi limited to glomerular capillaries. Hypertension
Proteasome inhibitors, e.g. bortezomib and carfilzomib	Renal impairment and hypertension with TMA Favourable response to stopping culprit drug
Pentostatin	Dose-dependent toxicity-mediated TMA at excessive doses
EGFR inhibitor cetuximab	Renal TMA, clinically nephrotic syndrome Resolved 2 months after stopping drug
IFN-β	Dose-dependent toxicity with endothelial hyperplasia, luminal occlusion and microaneurysm formation May occur years after drug initiation Variable recovery
Calcineurin inhibitors, e.g. ciclosporin and tacrolimus	Primarily affect glomerular arterioles Reducing the dose/stopping the drug can improve/reverse the TMA
Quinine	Idiosyncratic. Antibodies against platelets, leucocytes, erythrocytes and endothelial cells. Endothelial cell damage ?role of PEX
Oxymorphone hydrochloride (Opana ER)	IV abuse leads to renal TMA with cardiac and retinal ischemia
Emicizumab (in conjunction with bypassing agents)	Pathogenesis unknown ?XS thrombin generation leading to endothelial damage Stop drug, symptomatic management PEX used ?role Drug has been reintroduced on a resolution
Oestrogen-containing drugs, e.g. COC	Precipitation of congenital TTP and association with immune TTP

Adapted from [19]

Infections may present as a TMA. HIV can present with TTP with severe ADAMTS13 deficiency with immune-mediated pathogenesis. Many other infections may present with a TMA picture such as CMV, dengue, or even tuberculosis, and differential diagnosis requires a careful history, microbiological and virology assessment. Other infections such as influenza may be associated with the precipitation of iTTP or CM-HUS [19].

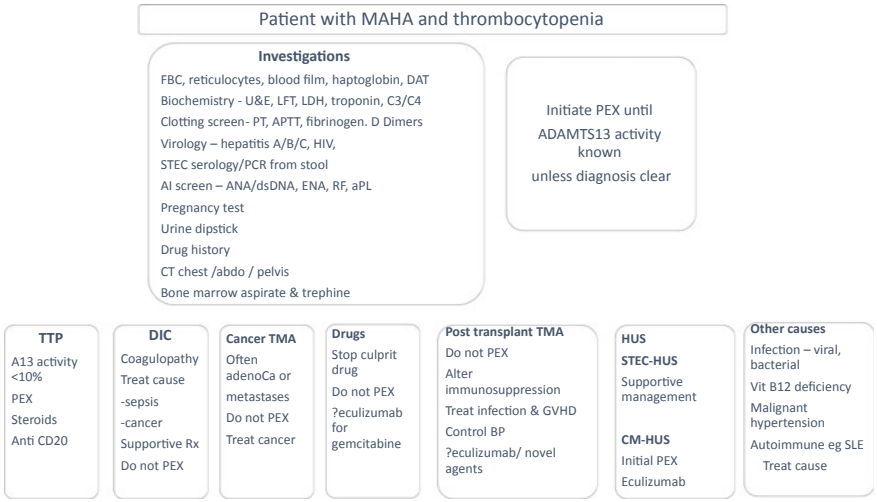

Fig. 10.1 Investigation and management of TMA in cancer patients

Other causes of TMA: An uncommon but highly treatable cause of a TMA picture is severe vitamin B12 deficiency. The presentation may appear identical to TTP, and PEX has even been initiated in some cases [25]. Other differential diagnoses to consider include malignant hypertension and autoimmune conditions such as lupus nephritis and vasculitides.

10.2 Investigation

Laboratory tests should be performed to confirm haemolysis and help to elucidate the underlying cause or precipitating factors (Fig. 10.1). The initial definition of a TMA remains a clinical one. However, the increasing availability of commercial ADAMTS13 assays means that confirmation/exclusion of the underlying diagnosis can occur in real time. ADAMTS13 activity levels <10% are in keeping with TTP, while ADAMTS13 activity levels between 10 and 20% require exclusion of anti-ADAMTS13 antibodies.

ADAMTS13 activity levels are typically within the middle or normal range in HUS [4]. Any reduction in ADAMTS13 levels in HUS is likely to be the result of consumption of ADAMTS13 due to raised VWF levels. A severe reduction in ADAMTS13 can be documented in severe sepsis-associated DIC, with increased UL VWF multimers, and related to the risk of renal failure [15]. ADAMTS13 is synthesised in the liver; therefore, any degree of liver failure may also lead to low ADAMTS13 activity. The differential between cancer-associated TMA, chemotherapy-associated TMA, and atypical HUS can be challenging, as all are diagnoses of exclusion and none are associated with severe ADAMTS13 deficiency.

10.3 Treatment

The initial treatment for TMAs is plasma exchange (PEX). This should be undertaken as soon as the diagnosis is considered, as TTP is a life-threatening disorder. The benefit of PEX in TTP has been confirmed in a randomised study [18], and PEX should be continued to remission in TTP patients. However, in other differential diagnoses, need for ongoing PEX will depend on response and the results of further laboratory investigations (Fig. 10.1).

The use of plasma exchange is not without risks, for example, central line insertion, infection, citrate toxicity, and reactions to plasma [24]. However, many of the investigations to identify the cause of the TMA should be available within 24–48 h from admission, and PEX can be stopped if another diagnosis is suggested for which PEX has no benefit. If TTP is confirmed by severe reduction in ADAMTS13 activity, further immunosuppressive therapy with steroids and anti-CD20 monoclonal antibody therapy are required.

Diagnosis of a cancer TMA is important as there is no beneficial role for PEX, steroids, or other immunosuppression used in TTP. The use of platelet transfusions for severe thrombocytopenia (normally withheld in TTP because of risk of worsening microthrombotic complications) would be appropriate in cancer TMA, following usual platelet transfusion thresholds. Treatment for anti-tumour therapy has been associated with improved survival in cancer TMA [10], but many patients have an extremely poor prognosis [14].

In evaluating patients with suspected TMA, chemotherapeutic agents and other drugs should be considered as a potential aetiology, and any potential culprit drug discontinued promptly. There is a very limited role for plasma exchange in drug-induced TMA as only a small proportion of cases (associated with ticlopidine) are associated with anti-ADAMTS13 antibodies. There are emerging case reports of complement inhibition [13, 23] and even anti-CD20 therapy being used to treat gemcitabine-induced TMA [17], but further data is required before any recommendation about these therapies can be made.

PEX is not of benefit in transplant-associated TMA (TA-TMA), and current first-line management includes discontinuation or alteration of the immunosuppressive regimen, treatment of coexisting infections and GVHD, aggressive hypertension control and supportive therapy. More recently, since an inherited or acquired defect in complement involved with endothelial damage [7] has been suggested, the use of complement inhibition with eculizumab has been described [6] as well as newer agents that target nitric oxide pathways [9].

Treatment of STEC-HUS is supportive. CM-HUS is initially a diagnosis of exclusion but is confirmed by finding mutations affecting the regulation of the alternative pathway of complement (present in about two-thirds of cases) [22]. The role of PEX in aHUS has, overall, not been confirmed as demonstrating a benefit. However, PEX at acute presentation is associated with an improvement in haematology parameters and often stabilisation of renal impairment [16]. Definitive

treatment of CM-HUS is with complement inhibition and, the earlier therapy is initiated, the better the renal outcome [12].

Management of other causes of TMA centres around treating the underlying condition, e.g. vitamin B12 injections for deficiency, BP control for malignant hypertension, and PEX, should be stopped.

In summary, the differential diagnosis of a TMA in a cancer patient is wide. Early exclusion of TTP (with the initiation of PEX until the diagnosis is excluded) is vital, but it is the precise diagnosis which drives appropriate and relevant therapy. The potential for drug-induced TMA should be considered and any potential causative agent avoided. Many of the causes of TMA seen in the oncology patient do not respond to plasma exchange.

References

1. Al-Nouri ZL, Reese JA, Terrell DR, Vesely SK, George JN (2015) Drug-induced thrombotic microangiopathy: a systematic review of published reports. Blood 125:616–618
2. Ducos G, Mariotte E, Galicier L, Canet E, Boutboul D, Lemiale V, Schlemmer B, Veyradier A, Azoulay E, Zafrani L (2014) Metastatic cancer-related thrombotic microangiopathies: a cohort study. Future Oncol 10:1727–1734
3. Elliott MA, Letendre L, Gastineau DA, Winters JL, Pruthi RK, Heit JA (2010) Cancer-associated microangiopathic hemolytic anemia with thrombocytopenia: an important diagnostic consideration. Eur J Haematol 85:43–50
4. Hassan S, Westwood JP, Ellis D, Laing C, McGuckin S, Benjamin S, Scully M (2015) The utility of ADAMTS13 in differentiating TTP from other acute thrombotic microangiopathies: results from the UK TTP Registry. Br J Haematol 171:830–835
5. Jodele S, Davies SM, Lane A, Khoury J, Dandoy C, Goebel J, Myers K, Grimley M, Bleesing J, El-Bietar J, Wallace G, Chima RS, Paff Z, Laskin BL (2014) Diagnostic and risk criteria for HSCT-associated thrombotic microangiopathy: a study in children and young adults. Blood 124:645–653
6. Jodele S, Fukuda T, Vinks A, Mizuno K, Laskin BL, Goebel J, Dixon BP, Teusink A, Pluthero FG, Lu L, Licht C, Davies SM (2014) Eculizumab therapy in children with severe hematopoietic stem cell transplantation-associated thrombotic microangiopathy. Biol Blood Marrow Transplant 20:518–525
7. Jodele S, Licht C, Goebel J, Dixon BP, Zhang K, Sivakumaran TA, Davies SM, Pluthero FG, Lu L, Laskin BL (2013) Abnormalities in the alternative pathway of complement in children with hematopoietic stem cell transplant-associated thrombotic microangiopathy. Blood 122:2003–2007
8. Kaidar-Person O, Nasrallah H, Haim N, Dann EJ, Bar-Sela G (2011) Disseminated carcinoma diagnosed by bone marrow biopsy in patients with microangiopathic hemolytic anemia and thrombocytopenia: a report of two cases with gastric cancer and a review of the literature. J Gastrointest Cancer 42:123–126
9. Khosla J, Yeh AC, Spitzer TR, Dey BR (2017) Hematopoietic stem cell transplant-associated thrombotic microangiopathy: current paradigm and novel therapies. Bone Marrow Transplant
10. Lechner K, Obermeier HL (2012) Cancer-related microangiopathic hemolytic anemia: clinical and laboratory features in 168 reported cases. Medicine (Baltimore) 91:195–205
11. Levi M, Toh CH, Thachil J, Watson HG (2009) Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. Br J Haematol 145:24–33

12. Licht C, Greenbaum LA, Muus P, Babu S, Bedrosian CL, Cohen DJ, Delmas Y, Douglas K, Furman RR, Gaber OA, Goodship T, Herthelius M, Hourmant M, Legendre CM, Remuzzi G, Sheerin N, Trivelli A, Loirat C (2015) Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome from 2-year extensions of phase 2 studies. Kidney Int 87:1061–1073
13. Lopez Rubio ME, Rodado Martinez R, Illescas ML, Mateo Bosch E, Martinez Diaz M, de la Vara Inesta L, Cabezuelo B, Morales Albuja ME, Lucas Guillen E, Jimeno Garcia L (2017) Gemcitabine-induced hemolytic-uremic syndrome treated with eculizumab or plasmapheresis: two case reports. Clin Nephrol 87(2017):100–106
14. Morton JM, George JN (2016) Microangiopathic hemolytic anemia and thrombocytopenia in patients with cancer. J Oncol Pract 12:523–530
15. Ono T, Mimuro J, Madoiwa S, Soejima K, Kashiwakura Y, Ishiwata A, Takano K, Ohmori T, Sakata Y (2006) Severe secondary deficiency of von Willebrand factor-cleaving protease (ADAMTS13) in patients with sepsis-induced disseminated intravascular coagulation: its correlation with development of renal failure. Blood 107:528–534
16. Phillips EH, Westwood JP, Brocklebank V, Wong EK, Tellez JO, Marchbank KJ, McGuckin S, Gale DP, Connolly J, Goodship TH, Kavanagh D, Scully MA (2016) The role of ADAMTS-13 activity and complement mutational analysis in differentiating acute thrombotic microangiopathies. J Thromb Haemost 14:175–185
17. Ritchie GE, Fernando M, Goldstein D (2017) Rituximab to treat gemcitabine-induced hemolytic-uremic syndrome (HUS) in pancreatic adenocarcinoma: a case series and literature review. Cancer Chemother Pharmacol 79:1–7
18. Rock GA, Shumak KH, Buskard NA, Blanchette VS, Kelton JG, Nair RC, Spasoff RA (1991) Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. N Engl J Med 325:393–397
19. Scully M (2017) Thrombocytopenia in hospitalized patients: approach to the patient with thrombotic microangiopathy. Hematology Am Soc Hematol Educ Program 2017:651–659
20. Scully M, Hunt BJ, Benjamin S, Liesner R, Rose P, Peyvandi F, Cheung B, Machin SJ (2012) Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol
21. Tallman MS, Kwaan HC (1992) Reassessing the hemostatic disorder associated with acute promyelocytic leukemia. Blood 79:543–553
22. Taylor CM, Machin S, Wigmore SJ, Goodship TH (2010) Clinical practice guidelines for the management of atypical haemolytic uraemic syndrome in the United Kingdom. Br J Haematol 148:37–47
23. Turner JL, Reardon J, Bekaii-Saab T, Cataland SR, ARANGO MJ (2016) Gemcitabine-associated thrombotic microangiopathy: response to complement inhibition and reinitiation of gemcitabine. Clin Colorectal Cancer
24. Vendramin C, McGuckin S, Alwan F, Westwood JP, Thomas M, Scully M (2017) A single-center prospective study on the safety of plasma exchange procedures using a double-viral-inactivated and prion-reduced solvent/detergent fresh-frozen plasma as the replacement fluid in the treatment of thrombotic microangiopathy. Transfusion 57:131–136
25. Yousaf F, Spinowitz B, Charytan C, Galler M (2017) Pernicious anemia associated cobalamin deficiency and thrombotic microangiopathy: case report and review of the literature. Case Rep Med 2017:9410727
26. Yui JC, van Keer J, Weiss BM, Waxman AJ, Palmer MB, D'Agati VD, Kastritis E, Dimopoulos MA, Vij R, Bansal D, Dingli D, Nasr SH, Leung N (2016) Proteasome inhibitor associated thrombotic microangiopathy. Am J Hematol 91:E348–E352

Thrombosis in the Philadelphia Chromosome-Negative Myeloproliferative Neoplasms

11

Kamya Sankar, Brady L. Stein and Raajit K. Rampal

Contents

K. Sankar
Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: kamya.sankar@northwestern.edu

B. L. Stein
Department of Medicine/Division of Hematology and Oncology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: brady.stein@nm.org

B. L. Stein
Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA

R. K. Rampal (✉)
Department of Medicine, Leukemia Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA
e-mail: rampalr@mskcc.org

G. Soff (ed.), *Thrombosis and Hemostasis in Cancer*, Cancer Treatment and Research 179, https://doi.org/10.1007/978-3-030-20315-3_11

11.1 Introduction

The myeloproliferative neoplasms (MPNs) are clonal stem cell-derived diseases [1]. The 2016 WHO classification for MPN includes polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic myeloid leukemia (CML), as well as chronic neutrophilic leukemia, chronic eosinophilic leukemia (not otherwise specified), and unclassifiable MPN. In this chapter, we will focus on PV, ET, and PMF, which are all subcategorized as the Philadelphia (Ph) chromosome-negative classical MPNs.

Our understanding of MPNs has greatly improved after discovery of the molecular genetic abnormalities associated with these diseases. Many MPN-associated mutations have been described, including driver mutations which activate the JAK-STAT pathway (most commonly *JAK2V617F*, followed by, *CALR* and *MPL* mutations), and additional somatic mutations (including, but not limited to *TET2, ASXL1, IDH1, IDH2, CBL, IKZF1, LNK*, and *EZH2*). These aid in diagnostic capabilities, contribute to understanding of disease pathogenesis, and inform prognosis [1, 2].

Common features among MPNs include tendencies toward myeloproliferation, splenomegaly, potential for progression to leukemia or myelofibrosis and thrombohemorrhagic events. It is well established that MPN patients have significantly elevated rates of arterial and venous thromboses when compared to the general population [3]. Thrombotic complications include microvascular events, which impact quality of life and macrovascular events (typically arterial > venous), which contribute to morbidity and prognosis. The pro-thrombotic and chronic inflammatory states contribute to the increased cardiovascular mortality in these patients. In the European Collaboration Study on Low-dose Aspirin in Polycythemia (ECLAP), cardiovascular mortality accounted for 45% of all deaths in PV patients,

whereas hematologic transformation accounted for 13% of deaths [4]. Accordingly, treatment strategies for the Ph-negative MPNs, especially ET and PV, are centered around prevention of incident and recurrent thrombohemorrhagic complications. In this chapter, we will discuss the epidemiology and prevalence, risk factors, potential surrogates or biomarkers, and treatment strategies for MPN-associated thrombosis.

11.2 Epidemiology, Prevalence and Types of Thrombosis

11.2.1 Prevalence

The general prevalence of major thrombosis at or prior to diagnosis of an MPN is estimated to be 34–38.6% in PV, 9.7–29.4% in ET, and 13% in PMF [5]. The cumulative rate of thrombosis after diagnosis of MPN is estimated to be approximately 3% per patient-year in PV and ET, and 2% per patient-year in PMF [6]. Recently, a large population-based cohort study in Sweden aimed to assess the risk for arterial and venous thrombosis in MPN compared to matched-control participants using the Sweden Cancer Registry between 1987 and 2009. This study confirmed that the rate of thrombosis is significantly higher in MPN patients as compared to the general population and peaks shortly after diagnosis of MPN [3].

This population-based cohort study reported a hazard ratio (HR) for overall thrombosis at one year of 2.5 (95% CI, 2.2–2.8), 2.2 (95% CI, 1.9–2.5), and 2.7 (95% CI, 2.2–3.2) in PV, ET, and PMF, respectively. The HRs for arterial thrombosis among patients with MPNs compared to the general population at 3 months, 1 year, and 5 years were 3.0 (95% CI, 2.7–3.4), 2.0 (95% CI, 1.8–2.2), and 1.5 (95% CI, 1.4–1.6), respectively. The HRs for venous thrombosis were 9.7 (95% CI, 7.8–12.0), 4.7 (95% CI, 4.0–5.4), and 3. 2 (95% CI, 2.9–3.6), respectively [3]. The rates of both arterial and venous thromboses were similar among the MPN subtypes, apart from a trend toward higher HRs for arterial thrombus shortly after diagnosis in PMF patients. In this study, arterial events were twice as common as venous events, similar to prior reports [3].

11.2.2 Overview of Thrombosis Type

Microvascular events in MPNs can include erythromelalgia, headaches, atypical chest pain, visual disturbances (e.g., amaurosis fugax, scotomata, and/or ophthalmic migraines), acral paresthesias, digital discoloration/ischemia, and livedo reticularis. Erythromelalgia is thought to reflect platelet hypersensitivity and manifests as a

Table 11.1 Risk factors for thrombosis in MPN

Risk factor	Study population	Findings
Conventional risk factors		
Age $\geq$ 60	Sweden Cancer Registry (1987–2009) $N = 9429$	HR for arterial and venous thromboses was 2.4 ($P < 0.001$)
	PV patients across 94 hematologic centers (international) $N = 1630$	Cardiovascular complications higher in PV patients $\geq$ 65 years ($P < 0.006$)
	WHO-defined ET patients across seven international centers $N = 891$	HR for major thrombosis was 1.5
History of thrombosis	Sweden Cancer Registry (1987–2009) $N = 9429$	HR for development of subsequent thrombotic event was 2.7 ($P < 0.001$)
	PV patients across 94 hematologic centers $N = 1630$	Cardiovascular complications higher in PV patients with history of thrombosis ($P = 0.0017$)
	WHO-defined ET patients across seven international centers $N = 891$	Patients with history of thrombosis had a significantly increased risk for developing subsequent thrombotic event (HR 1.93)
Cardiovascular risk factors	WHO-defined ET patients across seven international centers $N = 891$	Presence of cardiovascular risk factors gives HR of 1.6 for development of thrombosis
	WHO-defined low-risk PV patients across 7 international centers $N = 604$	Hypertension was associated with a nonsignificant increase in thrombotic risk, while tobacco use was associated with a significant increase in risk of arterial thrombosis (HR 1.9, $P = 0.012$)
Cell counts		
Erythrocytosis	*JAK2V617F* PV patients $N = 365$	Patients with less intense hematocrit control had higher risk of CV events (HR 3.9, $P = 0.007$)
Leukocytosis	PV patients across 94 hematologic centers $N = 1630$	WBC > 15×10^9/L correlated to increased risk of thrombosis (HR 1.71, $P = 0.017$)
Mutational status and allele burden		
JAK2V617F allele burden	WHO-defined PV patients $N = 173$	Allele burden > 75% associated with ↑ risk of major CV (RR 7.1, $P = 0.003$) and thrombotic events (RR 7.1, $P = 0.003$)
CALR mutation	ET patients $N = 107$	CALR-mutated patients had a lower risk of thrombosis compared to *JAK2* + patients ($P = 0.003$)

(continued)

Table 11.1 (continued)

Risk factor	Study population	Findings
CALR mutation	PMF patients *N* = 617	CALR-mutated PMF patients had a lower risk of thrombosis than JAK2-mutated PMF patients (*P* = 0.021)
Emerging risk factors		
CHIP mutations[a]	Patients with coronary heart disease *N* = 4726	CHIP carriers had a 1.9 × risk of coronary heart disease compared to non-carriers
Inflammatory markers	WHO-defined PV and ET patients *N* = 244	Major thrombosis was highest in the highest CRP tertile (*P* = 0.01) and lowest in the highest PTX-3 tertile (*P* = 0.045)
Biomarkers	Patients with PV and ET *N* = 32	Plasma *P*-selectin was significantly elevated in patients with PV and ET compared to healthy controls
	Patients with PV and ET *N* = 92	Patients with MPN had significantly increased microparticle levels as compared to healthy controls. Microparticle levels were also significantly increased in those who developed thrombosis

[a]Mutations in *JAK2, TET2, DNMT3A* and *ASXL1*

burning pain in the feet or hands, usually accompanied by erythema, pallor, or cyanosis. These events certainly impact quality of life, but do not influence prognosis.

Macrovascular thrombotic events associated with MPNs may occur in several locations. Examples include cerebrovascular accidents, cerebral venous thrombosis, transient ischemic attacks, renal artery or venous occlusion, coronary artery ischemia, deep vein thrombosis, pulmonary embolism, hepatic, portal, or splenic vein thrombosis, and superficial thrombophlebitis.

Abdominal vein thromboses (hepatic vein, portal vein, splenic vein, or mesenteric veins) are uniquely associated with MPNs. The prevalence of abdominal vein thrombosis ranges from 1 to 23% [7]. The disease-specific prevalence for PV, ET, and PMF is estimated to be 10, 13, and 1%, respectively [7]. In addition, MPNs are the most frequent underlying pro-thrombotic state in hepatic vein thrombosis (Budd–Chiari syndrome) and non-malignant, non-cirrhotic portal vein thrombosis. A systematic meta-analysis of the EMBASE and MEDLINE databases showed that the prevalence of MPNs is 40.9% in Budd–Chiari syndrome and 31.5% in non-cirrhotic portal vein thrombosis [8]. The presence of *JAK2V617F* was found in 41.1% of patients with Budd–Chiari syndrome and 27.7% of patients with non-cirrhotic portal vein thrombosis. PV was found to be more prevalent in Budd–Chiari syndrome as compared to portal vein thrombosis ($P = 0.001$) [8]. The high prevalence of MPNs and *JAK2V617F* in abdominal vein thromboses validates routine screening for *JAK2V617F* in the diagnostic workup of this patient

population, even in the absence of myeloproliferative features on blood count analysis (erythrocytosis, thrombocytosis, and leukocytosis). Cerebral venous thrombosis, to the contrary, is infrequent in MPN patients.

11.3 Risk Factors

The increased risk for MPN-thrombosis as compared to the general population likely rests upon many causes (Table 11.1). These include clinical characteristics, the presence of cardiovascular risk factors, an increase in blood cell counts (i.e., leukocytosis, erythrocytosis), inflammatory stress, mutational status and burden, and endothelial changes leading to upregulation of certain biomarkers [1].

11.3.1 Clinical Factors

The traditional risk factors for thrombosis in MPNs include advanced age (age $\geq$ 60) and history of a prior thrombotic event. In the large population-based cohort study mentioned above, though the risk for both arterial and venous thrombosis appeared to be elevated in patients with MPNs across all age groups, the HR for patients with MPNs aged 60 and older was 2.4 compared to patients younger than 60 (95% CI, 2.1–2.6, $P < 0.001$) [3]. In patients who had a history of thrombosis, HR for development of subsequent thrombotic event was 2.7 compared to those with no prior thromboses (95% CI, 2.5–2.9, $P < 0.001$). When combining the traditional risk factors, in patients who were aged 60 and older and had a history of thrombosis, the HR for thrombosis was 7.0 (95% CI, 6.2–8.0) [3].

The traditional risk factors have been supported by other studies as well. In the ECLAP study, the incidence of cardiovascular complications was higher in PV patients aged 65 and older (5.0% patient-years, $P < 0.006$) or with a history of prior thrombosis (4.93% patient-years, $P = 0.0017$) than in patients who were younger with no history of thrombosis (2.5% patient-years) [4]. In a large study of 891 patients with WHO-defined ET, the predictors for major thrombosis during a median follow-up of 6.2 years included age above 60 years (HR 1.5) and prior thrombosis (HR 1.93) [9]. The HR for arterial thrombosis in these patients was 1.7 for age greater than 60 and 2.1 for those with a history of thrombosis. Additional risk factors for predicting arterial thrombotic events included cardiovascular risk factors (HR 1.9), white blood cell count of greater than 11×10^9/L (HR 1.7), and the presence of the *JAK2V617F* mutation (HR 2.6) [9].

An exception includes younger women, who appear to be preferentially affected by splanchnic vein thrombosis [7]. In a retrospective analysis of 120 young patients with PV (age less than 45), compared to 84 older patients (age above 65), younger patients had similar overall rates of vascular complications compared to older patients (27 vs. 31%). However, there were significant differences when looking at the involved vascular bed. For example, splanchnic vein thrombosis occurred more

frequently in younger patients (13 vs. 2%, $P = 0.0056$) [10], most of whom where women. Women have also been shown to have higher rates of abdominal venous thromboses and comparable rates of all other vascular complications in another retrospective analysis of MPN patients. This was despite less prevalent dyslipidemia or smoking history, lower white blood cell (WBC) count and lower *JAK2* allele burden [11].

11.3.2 Cardiovascular Risk Factors

Hypertension, diabetes, dyslipidemia, and tobacco use are traditional risk factors for atherosclerosis. While important to manage, CV risk factors have been only variably associated with MPN-thrombosis risk. However, in ET, the presence of cardiovascular risk factors has been shown to be an independent risk factor for development of thrombosis and was included in a risk classification model for these patients. The "IPSET-thrombosis" score (and subsequently, the "revised IPSET-thrombosis" score) for ET was developed and validated in 2012. Previously, risk stratification for ET patients was two-tiered (low-risk vs. high-risk) and based on the traditional risk factors mentioned above (i.e., age and history of thrombosis). The IPSET-thrombosis model included additional independent factors: cardiovascular risk and *JAK2V617F* mutational status. In a cohort of 1220 patients, the presence of cardiovascular risk factors (HR 1.6) received one point in this classification, and the presence of *JAK2V617F* mutation (HR 2.0) received two points. This 3-tiered prognostic model (low-risk vs. intermediate-risk vs. high-risk) outperformed the 2-tiered conventional risk stratification in predicting vascular thrombotic events [12].

The results in PV have been more inconsistent. In one study, hypertension was associated with a nonsignificant increase in thrombotic risk, while smoking was associated with a significant increase in risk of arterial thrombosis (HR 1.9, 95% CI, 1.15–3.14, $P = 0.012$) [13]. Another study of the impact of arterial hypertension on thrombotic risk in low-risk PV patients revealed a nonsignificant correlation between hypertension and arterial events ($P = 0.09$). However, patients without hypertension had a thrombosis-free survival that was twice that of patients with hypertension. The frequency of hypertension in the group with the highest hematocrit was also significantly higher compared to the group with the lowest hematocrit ($P = 0.043$) [14]. This may be related to increased blood viscosity causing higher peripheral vascular resistance leading to increased frequency of hypertension. This study raises the notion that perhaps low-risk PV patients with hypertension should be considered as candidates for cytoreduction, though further prospective studies are required to support this.

11.3.3 Cell Counts

Both erythrocytosis and leukocytosis have been shown to increase thrombosis risk in MPNs. The association between erythrocytosis and thrombotic risk has been studied in PV. In the CYTO-PV study, 365 *JAK2*V617F-positive PV patients were randomized to more intensive treatment (with goal hematocrit of less than 45%) or less intensive treatment (with target hematocrit of 45–50%), using phlebotomy and/or hydroxyurea. During a median follow-up period of 31 months, those with hematocrit less than 45% had a significantly lower rate of cardiovascular death and major thrombosis than those with a higher hematocrit target (HR 3.9, $P = 0.007$). Patients in the higher hematocrit target group also had a higher white blood cell count, which may have been a confounding cause of thrombosis, but otherwise, there was no significant heterogeneity found according to age, prior thrombosis, splenomegaly, or prior therapies. This study confirmed that PV patients should be treated to a goal hematocrit of less than 45% [15].

Baseline leukocytosis in both PV and ET patients has been shown to be an independent risk factor for thrombosis [16]. In a study involving the ECLAP database, PV patients with a WBC count greater than 15×10^9/L compared to less than 10×10^9/L had a significant increase in risk of thrombosis (HR 1.71, $P = 0.017$), mainly deriving from increased risk of myocardial infarction (HR 2.84, $P = 0.013$). Leukocytosis associated more with arterial than venous thrombosis. The presence of inflammatory stimuli may partially account for the association between leukocytosis and vascular risk.

Thrombocytosis, on the other hand, has been usually associated with bleeding, particularly when platelet count is greater than 1000×10^9/L to 1500×10^9/L. The association between thrombocytosis and bleeding may be mediated by the development of acquired von Willebrand disease. In a study with 69 ET patients compared to 69 controls and 10 patients with reactive thrombocytosis, the von Willebrand factor activity-to-antigen ratio was significantly reduced in ET patients by $35 \pm 17\%$ ($P < 0.001$) [17]. In a different study, a major reduction in large von Willebrand factor multimers was shown in ET patients with platelet count of greater than 1000×10^9/L [18]. Therefore, patients with extreme thrombocytosis should be screened for acquired von Willebrand disease, prior to consideration of antiplatelet therapy, and especially in the setting of bleeding symptoms.

11.3.4 Mutational Status and Burden

The driver mutations in PV, ET, and PMF include *JAK2 V617F (*and in PV, occasionally, *JAK2* exon 12*)*, *CALR*, and *MPL* mutations. There are clear differences in thrombosis risk by driver mutational status in ET. In this MPN subtype, those with *CALR* mutations have a lower risk of thrombosis as compared to those with the *JAK2* V617F mutation ($P = 0.003$) [19]. *JAK2*-mutated ET patients and *JAK2*-mutated PV patients have a similar risk of thrombosis which is twice as high as those with *CALR* mutation [20]. In addition, when assessing ET patients by

means of IPSET-thrombosis score and mutational status, the *CALR* patients and "triple-negative" (absence of any driver mutation) patients more frequently belonged to the low-risk group by IPSET and had a significantly more favorable thrombosis-free rate than those with the *JAK2* mutation ($P < 0.001$) [21].

The *JAK2* allele burden has been considered as a novel means of stratifying PV patients for risk of cardiovascular events. In a study of 173 PV patients, a *JAK2* allele burden of greater than 75% was found to be significantly associated with risk of major cardiovascular events (RR 7.1, $P = 0.003$) and thrombotic events (RR 7.1, $P = 0.003$). In a multivariate analysis including age, previous thrombosis, and leukocytosis, the *JAK2* allele burden was still found to be significantly associated with cardiovascular events ($P = 0.039$) [22].

In PMF patients, those with *CALR* mutations have a lower risk of thrombosis than those with *JAK2* mutations ($P = 0.021$), which remained significant after adjusting for age. The *CALR*-mutated PMF patients additionally had a lower risk of anemia, thrombocytopenia, and leukocytosis. Not surprisingly, the estimated risk of thrombosis is twofold higher in *JAK2*-mutated PMF patients as compared to *CALR*-mutated PMF patients [23].

11.3.5 CHIP Mutations

Somatic mutations and cytopenias have been described in patients in the absence of an established diagnosis of a primary marrow disorder. Clonal hematopoiesis of indeterminate potential (CHIP) refers to a context in which somatic mutations are identified in individuals who do not yet meet criteria for a hematologic neoplasm. Idiopathic cytopenia of undetermined significance (ICUS) refers to patients who have single or multiple cytopenias in the absence of an identified clonal mutation. Clonal cytopenia of undetermined significance (CCUS) refers to patients who have an identified clonal mutation as well as one or more cytopenias, again in the absence of an established hematologic neoplasm.

The most common clonal mutations include mutations in JAK2, *DNMT3A*, *TET2*, and *ASXL1*. These mutations are usually identified in older patients. Patients with CHIP have ten times the risk of hematologic cancers, and interestingly, are at increased risk for coronary heart disease, and at increased risk of death from any cause [24]. From two prospective cohorts, carriers of CHIP had a 1.9-fold increased risk of coronary heart disease. In two retrospective cohorts, the risk of myocardial infarction was fourfold. CHIP patients with the *JAK2* mutation had 12.1 times the risk of incidence of coronary artery disease as compared to those with no mutations [24]. The association between CHIP mutations and coronary artery disease may be mediated by inflammatory responses. Importantly, in addition to driver mutations, MPN patients may also have mutations in *TET2, DNMT3A,* and *ASXL1*. Whether the presence of these additional somatic mutations adds to thrombotic risk is not yet established.

11.3.6 Inflammatory Stress

Other biomarkers have also correlated inflammation with thrombosis risk. For example, hs-CRP and PTX-3 are biomarkers which may be useful to improve upon vascular risk assessment in MPN patients. Among 244 patients with PV and ET, the major thrombosis rate was significantly and independently increased with high levels of hs-CRP [25]. In another study of 305 ET patients and 172 PV patients, hs-CRP levels were independent of mutational profile and also found to be an independent risk factor for major thrombosis (OR 2.57). On the other hand, high levels of PTX-3 have been associated with a lower risk of thrombosis [26]. It is possible that PTX-3 may have a protective role against the detrimental effects of inflammation in cardiovascular risk. In yet another study of 244 patients with ET and PV, the highest hs-CRP tertile as compared to the lowest correlated with the presence of cardiovascular risk factors ($P = 0.012$) and *JAK2* allele burden of greater than 50% ($P = 0.045$). Major thrombosis was highest in the highest CRP tertile ($P = 0.01$) and lower at the highest PTX-3 tertile ($P = 0.045$) [27].

11.3.7 Biomarkers

Platelet activation leads to increased expression of certain biomarkers which have been investigated in MPN-thrombosis. For example, platelet activation leads to increased expression of *P*-selectin, thrombospondin, and activated fibrinogen receptor (GPIIb/IIIa), which has been found to correlate with thrombosis. Enhanced platelet activation has been demonstrated in PV and ET patients. Platelet interaction with other blood components has the capacity to provoke endothelial activation and/or damage. A marker of leukocyte, platelet, and endothelial cell activation is the family of adhesion molecules known as selectins. In patients with PV and ET, increased levels of soluble plasma selectins were observed as compared to healthy controls [28].

Platelets and vascular endothelial cells produce pro-coagulant microparticles, which may lead to the hypercoagulable state found in MPNs [29]. In a study of 92 MPN patients, microparticle levels were found to be significantly increased as compared to controls. In addition, microparticle levels were significantly increased in those patients who developed thrombosis [30].

An increase in global thrombin generation due to an acquired activated protein C (APC) resistance may also contribute to the pro-thrombotic state of MPNs [29]. Alteration of coagulation proteins induces an APC-resistant phenotype in these patients. By use of a thrombin generation assay, an APC-resistant phenotype has been shown in ET and PV patients, particularly in *JAK2V617F* carriers [31]. Allele burden correlated with higher thrombin generation [32]. The role of these biomarkers in assessing thrombosis risk has yet to be validated, would ideally require prospective trials before entering into clinical practice.

Table 11.2 Treatment strategies to reduce MPN-thrombosis risk

Treatment	Findings	Comment
Antiplatelet therapy	Arterial and venous thrombosis risk reduction in PV	Recommended in the absence of contraindication for PV pts Inconsistent evidence in ET No prospective data in PMF
Phlebotomy	Reduction in CV event rate in PV	Hematocrit target 45% or less now established
Cytoreduction	Randomized data supports frontline use of HU for high-risk ET No randomized data for use of HU in PV, but typically frontline based on consensus	Recommended for high-risk ET and PV patients, or in low-risk patients with uncontrolled symptoms, symptomatic thrombocytosis, progressive leukocytosis HU, interferons frontline in PV; some consider anagrelide as frontline in ET (along with HU and IFNs)
Anticoagulation	Recommended as per standard guidelines for management of venous thrombosis	Choice of agent and duration of anticoagulation remain heterogeneous Scarce evidence regarding use of DOACs
Plateletpheresis	Consensus recommendation in the setting of symptomatic thrombocytosis with thrombotic event	Contemporary use less common, given access to cytoreduction, and lack of strong association between thrombocytosis and thrombosis
Abdominal venous thrombosis	Prevalent in younger women, MPN often occult	Consensus recommendation for indefinite anticoagulation, co-management with hepatology
Pregnancy	No evidence to support that therapeutic maneuvers reduce risk for adverse maternal/fetal outcomes Literature in ET > PV > MF	Low-dose aspirin in low-risk patients Hematocrit control in pregnant PV patients Enoxaparin postpartum in low-risk patients Antepartum enoxaparin in high-risk patients IFN is cytoreductive of choice (consensus) if required (previously on cytoreduction, symptomatic thrombocytosis)
Perioperative state	Risk for thrombosis or hemorrhage around 8%, despite aggressive count control	Blood count control for elective surgeries VTE prophylaxis when appropriate Antiplatelet use post-cardiovascular or vascular procedures Hematology co-management

11.4 Treatment

The survival in WHO-defined ET patients is near normal, with an estimated 15-year survival of approximately 80%. In WHO-defined PV, 10-year projected rates for survival are > 75%. However, the risk of thrombosis exceeds 20%, and many patients additionally develop microvascular disturbances which interfere with quality of life. Treatment for these classical MPNs is principally aimed at preventing thrombohemorrhagic complications [33] (Table 11.2).

11.4.1 PV

Patients with PV should be managed with low-dose aspirin and phlebotomy to maintain hematocrit at less than 45% [34]. Currently, the conventional model of risk stratification in PV which categorizes patients as "low-risk" or "high-risk" is recommended. The presence of either age above 60 and/or history of thrombosis defines a high-risk patient [35]. In PV, low-dose aspirin is indicated in all patients who do not have a contraindication, regardless of risk category [36]. In a multicenter double-blinded randomized control trial, PV patients were randomized to either placebo or 100 mg of aspirin. After a median follow-up of 3 years, aspirin was shown to reduce the combined primary end point (RR 0.4, 95% CI, 0.18–0.91, $P = 0.027$), which included cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and major venous thromboembolism, without increasing risk of bleeding as compared to placebo [37].

Phlebotomy is another cornerstone of treatment for PV and is used to maintain hematocrit at less than 45% in PV patients. The multicenter randomized clinical trial "CYTO-PV" showed a reduction in the primary end point of cardiovascular death and major thrombosis when hematocrit was maintained at a target of less than 45% as compared to a higher goal of 45–50% (HR in the high-hematocrit group = 3.91, $P = 0.007$). This study supported the use of phlebotomy to maintain a hematocrit of less than 45% in PV patients in order to prevent thrombosis.

Cytoreductive therapy is indicated if patients have poor tolerance to phlebotomy, symptomatic or progressive splenomegaly, severe symptoms, platelet counts greater than 1500×10^9/L and/or progressive leukocytosis [34]. Options for cytoreductive therapy include hydroxyurea or interferon-alpha. In PV, there are no contemporary randomized trials proving that hydroxyurea modifies risk for thrombosis; rather, use is based on prior PVSG studies, tolerability, perceived safety, and consensus recommendations. A prior phase 2 study suggested that pegylated interferon may reduce risk for thrombosis, as no events were observed over a short follow-up. Phase 3 studies comparing hydroxyurea and pegylated interferon (as well as a novel interferon, Ropeginteferon) are underway [38]. Preliminarily, non-inferiority has been suggested, when comparing these two strategies, but detailed analysis regarding thrombosis event rates are not yet published. Ruxolitinib is a second-line option if there was an inadequate response to hydroxyurea [39]. Thrombotic events

were not analyzed as part of a primary or secondary end point, but fewer events were reported in the ruxolitinib arm, compared to best available therapy [40]. In addition, cardiovascular risk factors (i.e., tobacco use, hypertension, hyperlipidemia, diabetes) must be aggressively managed.

11.4.2 ET

Most recently, the "revised IPSET-thrombosis" model was developed to assess vascular risk in ET patients. This model includes thrombotic history, age above 60, and *JAK2V617F* mutational status. Using such variables, there are four risk categories: "very low-risk" (no adverse features), "low-risk" (presence of *JAK2V617F* only), "intermediate-risk" (presence of age above 60 only), and "high-risk" (presence of thrombosis history or presence of both *JAK2V617F* and advanced age). This classification was then validated in a study with 585 ET patients. Thrombosis-free survival from time of diagnosis to first thrombotic event after diagnosis was calculated, and patients were grouped according to conventional stratification (two-tiered), "IPSET-thrombosis" (three-tiered), and the "revised IPSET-thrombosis" (four-tiered) models. There was a significant difference in thrombosis-free survival between the "very low-risk" and "low-risk" groups ($P = 0.024$), as well as the "intermediate-risk" compared to the "high-risk" groups ($P = 0.03$) [33]. This validated model may provide useful information in ET patients regarding thrombotic risk and can be used to direct treatment. Typically, cytoreductive therapy would be reserved for the high-risk group. Additionally, those falling into lower risk groupings, but with uncontrolled vascular symptoms (or bleeding due to thrombocytosis) would be candidates for cytoreduction.

Unlike in PV, there are no randomized, controlled trials to support aspirin use in ET patients. In 433 low-risk ET patients, antiplatelet therapy did not affect the risk of thrombosis in *CALR*-mutated ET patients, however, was associated with a higher incidence of bleeding. In comparison, aspirin reduced the incidence of venous thrombosis in *JAK2V617F*-mutated ET patients, without increasing the risk of bleeding. Therefore, antiplatelet therapy may be of benefit in *JAK2*-mutated ET patients [41]. This was replicated in another study of patients with low-risk ET who either received antiplatelet monotherapy or observation [42]. *JAK2*-mutated ET patients not receiving antiplatelet therapy had an increased risk of venous thrombosis (IRR 4, $P = 0.02$). In addition, patients with known cardiovascular risk factors had increased rates of arterial thrombosis while on observation (IRR 2.5, $p = 0.04$). Increased risk of bleeding was only seen in patients with platelet count of greater than 1000×10^9/L while under antiplatelet therapy (IRR 5.4, $P = 0.004$). However, the effect of antiplatelet therapy still remains unknown. In a systematic meta-analysis involving 24 observational studies with 6153 ET patients, the findings were imprecise and inconsistent [43]. The reported relative risks for thrombosis or bleeding while on antiplatelet therapy showed wide confidence intervals. In addition, certainty was rated low or very low for all outcomes. Therefore, antiplatelet therapy may be an indication for reduction in VTE in *JAK2*-mutated ET patients and reduction in rate of arterial

thromboses in patients with known cardiovascular risk factors. In the remaining patients, observation may be an adequate option.

Unlike in PV, there have been two randomized controlled trials involving hydroxyurea in high-risk ET patients. In 114 patients with high-risk ET randomized to hydroxyurea versus observation, hydroxyurea was effective at preventing thrombosis in high-risk ET patients ($P = 0.003$) [44]. High-risk ET patients should be treated with cytoreductive therapy though the choice of cytoreductive agent remains unclear. In 809 patients with high-risk ET randomized to low-dose aspirin plus either anagrelide or hydroxyurea, hydroxyurea plus aspirin reduced the composite end point of arterial and venous thrombosis as compared to anagrelide plus aspirin ($P < 0.01$) [45]. In a subsequent randomized control trial (the "ANAHYDRET" trial), 259 previously untreated high-risk ET patients were treated with either anagrelide or hydroxyurea. Anagrelide was shown to be non-inferior to hydroxyurea after a 36-month observation period, and there was no significant difference between the groups in incidences of thromboses or bleeding events [46]. Society guidelines differ. The NCCN includes hydroxyurea, interferons, and anagrelide as first-line choices; ELN guidelines offer anagrelide as a second-line option. As with PV, pegylated interferon is under evaluation in ET; again, detailed analysis regarding thrombosis risk reduction from phase 2 and phase 3 consortium studies are not yet published. Ruxolitinib is not recommended in ET. In 110 ET patients who were resistant to hydroxyurea, a randomized control trial comparing ruxolitinib to best available therapy did not show any evidence of improvement in complete response within one year (46.6 vs. 44.2%, $P = 0.40$) [47]. In addition, the rates of thrombosis, hemorrhage, and hematologic transformation were not significantly different at two years. Platelet-lowering treatment should be considered at platelet counts greater than 1500×10^9/L in order to reduce the risk of bleeding. Again, cardiovascular risk factors must be aggressively managed.

11.4.3 Anticoagulation Therapy

Anticoagulation therapy is indicated for those patients who develop venous thrombosis. The choice of anticoagulant and appropriate duration of therapy, however, is unclear. Some advise long-term anticoagulation given the intrinsic thrombophilic nature of MPNs, which may represent an ongoing/permanent risk factor for recurrence. Even hematologists who specialize in MPN lack consensus in long-term treatment of thrombosis in MPN patients. In a survey-based study of hematologists who primarily treated patients with MPNs, the duration of anticoagulation and/or use of aspirin varied [48]. Overall, there was a tendency to prolong treatment with aspirin in those with arterial thrombosis, whereas in patients with venous thrombosis, there was a tendency for more prolonged treatment with a vitamin K antagonist (VKA) with or without aspirin. There was no statistical difference between any of the treatment choices and no association between physician expertise, volume of patients, or years of practice to treatment choice.

In one study, the risk of thrombotic recurrence in ET or PV patients treated with VKAs for arterial or venous thrombosis was analyzed. The decision on duration of VKA therapy was made by the attending physician on the basis of clinical guidelines at that time. After an observation period of 7.7 years, there was a 2.8-fold reduction in the risk of thrombotic recurrence ($P < 0.0005$) in the VKA-treated group, without any higher incidence of bleeding. Direct oral anticoagulants (DOAC) have not been well studied in MPNs. In a single-institutional registry of 760 MPN patients, 25 had been treated with a DOAC. After a median follow-up of 2.1 years, this case–control study did not detect a significant difference in thrombotic or hemorrhagic events between patients treated with low-dose aspirin and DOACs [49]. Therefore, DOACs may be efficient and safe for use in MPN patients, however further prospective randomized control studies are required.

Abdominal vein thrombosis, which includes hepatic vein occlusion, extrahepatic portal vein occlusion, and mesenteric vein thrombosis, is strongly associated with MPNs. Indefinite anticoagulation is typically indicated in these patients, based on consensus recommendations. The general consensus for treatment includes low molecular weight heparin followed by indefinite oral anticoagulation. Usually, these patients require joint management with hepatology, for surveillance and management of esophageal varices, which follow with portal hypertension. In addition, in those with thrombocytosis, erythrocytosis, and/or leukocytosis, cytoreductive therapy should be used to normalize counts.

11.4.4 Plateletpheresis

Though cytoreductive therapy remains the mainstay of therapy for extreme thrombocytosis, plateletpheresis may be offered as a temporizing measure in certain instances where rapid reduction in platelet count is required. In a case-based review of plateletpheresis in the management of extreme thrombocytosis in MPNs, plateletpheresis was successfully used in patients for the following indications: neurological symptoms due to transient thromboembolic episode, hyperthrombocytosis-related acquired von Willebrand disease, as a prophylactic measure to reduce platelet counts below a particular range, and for symptomatic relief in context of an ischemic toe [50]. Though data on clinical utility of plateletpheresis is largely case report-based, this treatment modality may be an option for patients with extreme thrombocytosis complicated by a thrombohemorrhagic event, when rapid reduction is required prior to emergent surgery, or when cytoreductive agents are contraindicated. The decision to use plateletpheresis is individualized to the patient and clinical scenario. In asymptomatic ET patients, current guidelines do not specify a platelet count threshold at which apheresis should be performed. In patients with counts above 1500×10^9/L, plateletpheresis should be considered due to increased risk of major hemorrhage related to an acquired von Willebrand deficiency [51].

11.4.5 High-Risk Situations

11.4.5.1 Pregnancy

There is an increased risk of miscarriages and other complications of pregnancy such as abruptio placentae, pre-eclampsia, and intra-uterine growth retardation associated with MPN. The fetal loss is estimated to be 3–4-fold higher as compared to the general population [34]. Additional risk factors include prior pregnancy complication and potentially the presence of *JAK2* mutation. In general, for low-risk pregnancies, the target hematocrit should be less than 45% in those with PV. Low-dose aspirin is given for prophylaxis, and low molecular weight heparin may be advised postpartum, especially after cesarean section. In high-risk pregnancies, consideration for antepartum LMWH should be given. One could consider interferon-alpha therapy if previously on cytoreduction (hydroxyurea cannot be used during pregnancy) or if the platelet count exceeds $1500 \times 10^9/L$[41].

11.4.5.2 Surgery

MPN patients are considered high-risk surgical candidates due the increased risk of thrombohemorrhagic complications in the perioperative period. Currently, there are no definitive guidelines for the perioperative management of MPN patients. A multicenter retrospective analysis to estimate thrombosis and hemorrhage after 311 surgical procedures in patients with PV and ET showed that there was variability in the use of perioperative prophylaxis (54.3% received subcutaneous heparin and 15.4% received antiplatelet therapy). During the 3-month follow-up period, there were 12 arterial thrombotic events, 12 venous thrombotic events, 23 major and seven minor hemorrhages, and five deaths [52]. There was no correlation between bleeding episodes, type of diagnosis, use of antithrombotic prophylaxis, or type of surgery. Further investigations are required for optimal management of these patients.

11.5 Conclusions

Patients with MPNs are at increased risk for both arterial and venous thrombosis as compared to the general population [3]. These include microvascular and macrovascular events which lead to increased morbidity and mortality. In addition to the traditional risk factors of older age (age above 60) and history of prior thrombosis, many factors, including mutational status, contribute to this pro-thrombotic state found in MPNs. The MPNs also induce a chronic inflammatory state which leads to increased cardiovascular mortality in these patients [4]. Treatment is based on thrombotic risk assessment. Treatment strategies are aimed at preventing thrombohemorrhagic complications and include aspirin, phlebotomy, cytoreductive therapies, and anticoagulation therapy. Future direction in MPN research will hopefully identify more precise and personalized surrogates/biomarkers for thrombosis risk and clarify whether or not novel therapies, such as JAK inhibitors or interferons reduce risk for thrombosis.

References

1. Barbui T, Finazzi G, Falanga A (2013) Myeloproliferative neoplasms and thrombosis. Blood 122(13):2176–2184
2. Tefferi A, Vainchenker W (2011) Myeloproliferative neoplasms: Molecular pathophysiology, essential clinical understanding, and treatment strategies. J Clin Oncol 29(5):573–582
3. Hultcrantz M, Björkholm M, Dickman PW, Landgren O, Derolf ÅR, Kristinsson SY, Andersson TML (2018) Risk for arterial and venous thrombosis in patients with myeloproliferative neoplasms: a population-based cohort study. Ann Intern Med. [Epub ahead of print 16 January 2018]
4. Marchioli R, Finazzi G, Landolfi R, Kutti J, Gisslinger H, Patrono C, Marilus R, Villegas A, Tognoni G, Barbui T (2005) Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. J Clin Oncol 23(10):2224–2232
5. Tefferi A, Elliott M (2007) Thrombosis in myeloproliferative disorders: prevalence, prognostic factors, and the role of leukocytes and JAK2V617F. Semin Thromb Hemost 33:313–320
6. McMahon B, Stein BL (2013) Thrombotic and bleeding complications in classical myeloproliferative neoplasms. Semin Thromb Hemost 39(1):101–111
7. Gangat et al (2006) Abdominal vein thrombosis in ET: prevalence, clinical correlates and prognostic implications. Eur J Haematol 77:323–333
8. Smalberg et al (2012) Myeloproliferative neoplasms in Budd-Chiari Syndrome and portal vein thrombosis: a meta-analysis. Blood 120(25):4921–4928
9. Carobbio et al (2011) Risk factors for arterial and venous thrombosis in WHO-defined essential thrombocythemia: an international study of 891 patients. Blood 117(22):5857–5859
10. Stein BL, Saraf S, Sobol U, Halpern A, Shammo J, Rondelli D, Michaelis L, Odenike O, Rademaker A, Zakarija A, McMahon B, Spivak JL, Moliterno AR (2013) Age-related differences in disease characteristics and clinical outcomes in polycythemia vera. Leuk Lymphoma 54(9):1989–1995
11. Stein BL, Saraf S, Sobol U, Halpern A, Shammo J, Rondelli D, Michaelis L, Odenike O, Rademaker A, Zakarija A, McMahon B, Spivak JL, Moliterno AR (2011) Gender and vascular complications in the JAK2 V617F-positive myeloproliferative neoplasms. Thrombosis (article ID 874146)
12. Barbui T, Finazzi G, Carobbio A, Thiele J, Passamonti F, Rumi E, Ruggeri M, Rodeghiero F, Randi ML, Bertozzi I, Gisslinger H, Buxhofer-Ausch V, De Stefano V, Betti S, Rambaldi A, Vannucchi AM, Tefferi A (2012) Development and validation of an International Prognostic Score of Thrombosis in WHO-ET (IPSET-Thrombosis). Blood 120(26):5128–5133
13. Landolfi R, Di Gennaro L, Barbui T, De Stefano V, Finazzi G, Marfisi R, Tognoni G, Marchioli R (2007) Leukocytosis as a major thrombotic risk factor in patients with PV. Blood 109(6):2446–2452
14. Barbui T, Vannucchi AM, Carobbio A, Rumi E, Finazzi G, Gisslinger H, Ruggeri M, Randi ML, Cazzola M, Rambaldi A, Gisslinger B, Pieri L, Thiele J, Pardanani A, Tefferi A (2017) The effect of arterial hypertension in low-risk polycythemia vera. Am J of Hematology 92(1):E5
15. Barbui T, Carobbio A, Cervantes F, Vannucchi AM, Guglielmelli P, Antonioli E, Alvarez-Larrán A, Rambaldi A, Finazzi G, Barosi G (2010) Thrombosis in primary myelofibrosis: incidence and risk factors. Blood 115(4):778–782
16. Barbui T et al (2009) Perspective on thrombosis in essential thrombocythemia: is leukocytosis a causative factor? Blood 114:759–763
17. Lancellotti S, Dragani A, Ranalli P, Petrucci G, Basso M, Tartaglione R, Rocca B, De Cristofaro R (2015) Qualitative and quantitative modifications of vWF In patients with ET and controlled platelet count. J Thromb Haemost 13:1226–1237
18. van Genderen PJ, Budde U, Michiels JJ, van Strik R, van Vliet HH (1996) The reduction of large vWF multimers in plasma in ET is related to platelet count. Br J Haematol 93:962–965

19. Klampfl T, Gisslinger H, Harutyunyan AS, Nivarthi H, Rumi E, Milosevic JD, Them NC, Berg T, Gisslinger B, Pietra D, Chen D, Vladimer GI, Bagienski K, Milanesi C, Casetti IC, Sant'Antonio E, Ferretti V, Elena C, Schischlik F, Cleary C, Six M, Schalling M, Schönegger A, Bock C, Malcovati L, Pascutto C, Superti-Furga G, Cazzola M, Kralovics R (2013) Somatic mutations of calreticulin in myeloproliferative neoplasms. N Engl J Med 369 (25):2380–2390
20. Rumi E, Pietra D, Ferretti V, Klampfl T, Harutyunyan AS, Milosevic JD, Them NC, Berg T, Elena C, Casetti IC, Milanesi C, Sant'antonio E, Bellini M, Fugazza E, Renna MC, Boveri E, Astori C, Pascutto C, Kralovics R, Cazzola M (2014) Jak2 or CALR mutation status defines subtypes of ET with substantially different clinical courses and outcomes. Blood 123 (10):1544–1551
21. Bertozzi I, Peroni E, Coltro G, Bogoni G, Cosi E, Santarossa C, Fabris F, Randi ML (2016) Thrombotic risk correlates with mutational status in ET. Eur J Clin Inv 46(8):683–689
22. Vannucchi AM, Antonioli E, Guglielmelli P, Longo G, Pancrazzi A, Ponziani V, Bogani C, Ferrini PR, Rambaldi A, Guerini V, Bosi A, Barbui T (2007) Prospective identification of high-risk polycythemia vera patients based on Jak2V617F allele burden. Leukemia 21:1952–1959
23. Rumi E, Pietra D, Pascutto C, Guglielmelli P, Martínez-Trillos A, Casetti I, Colomer D, Pieri L, Pratcorona M, Rotunno G, Sant'Antonio E, Bellini M, Cavalloni C, Mannarelli C, Milanesi C, Boveri E, Ferretti V, Astori C, Rosti V, Cervantes F, Barosi G, Vannucchi AM, Cazzola M (2014) Clinical effect of driver mutations of JAK2, CALR, and MPL in primary myelofibrosis. Blood 24(7):1062–1069
24. Jaiswal S, Natarajan P, Silver AJ, Gibson CJ, Bick AG, Shvartz E, McConkey M, Gupta N, Gabriel S, Ardissino D, Baber U, Mehran R, Fuster V, Danesh J, Frossard P, Saleheen D, Melander O, Sukhova GK, Neuberg D, Libby P, Kathiresan S, Ebert BL (2017) Clonal Hematopoiesis and risk of atherosclerotic cardiovascular disease. N Engl J Med 377(2):111–121
25. Lussana F, Rambaldi A (2017) Inflammation and myeloproliferative neoplasms. J Autoimmun 85:58–63
26. Lussana F, Carobbio A, Salmoiraghi S, Guglielmelli P, Vannucchi AM, Bottazzi B, Leone R, Mantovani A, Barbui T, Rambaldi A (2017) Driver mutations, pentraxin-3 and C-reactive protein in essential thrombocythemia and polycythemia vera. J Hematol Oncol 10:54
27. Barbui T, Carobbio A, Finazzi G, Vannucchi AM, Barosi G, Antonioli E, Guglielmelli P, Pancrazzi A, Salmoiraghi S, Zilio P, Ottomano C, Marchioli R, Cuccovillo I, Bottazzi B, Mantovani A, Rambaldi A (2011) Inflammation and thrombosis in essential thrombocythemia and polycythemia vera: different role of CRP and pentraxin 3. Hematologica 96(2):315–318
28. Vianello F, Battisti A, Cella G, Marchetti M, Falanga A (2011) Defining the thrombotic risk in patients with myeloproliferative neoplasms. Sci World J 11:1131–1137
29. Falanga A et al (2012) Thrombotic disease in the myeloproliferative neoplasms. Hematology Am Soc Hematol Educ Program. 2012:571–581
30. Zhang W, Qi J, Zhao S, Shen W, Dai L, Han W, Huang M, Wang Z, Ruan C, Wu D, Han Y (2017) Clinical significance of circulating microparticles in Ph-myeloproliferative neoplasms. Oncol Lett 14:2531–2536
31. Marchetti M, Castoldi E, Spronk HM, van Oerle R, Balducci D, Barbui T, Rosing J, Ten Cate H, Falanga A (2008) Thrombin generation and APC resistance in patients with ET and PV. Blood 112(1):4061–4068
32. Tevet M, Ionescu R, Dragan C, Lupu AR (2015) Influence of the Jak2V617F mutation and inherited thrombophilia on the thrombotic risk among patients with myeloproliferative disorders. Maedica 10(1):27–32
33. Haider M, Gangat N, Lasho T, Abou Hussein AK, Elala YC, Hanson C, Tefferi A (2016) Validation of the revised international prognostic score of thrombosis for essential thrombocythemia (IPSET-thrombosis) in 585 Mayo clinic patients. Am J Hematol 91 (4):390–394

34. Barbui et al (2011) Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European Leukemia Net. J Clin Oncol 29 (6):761–769
35. Tefferi A et al (2013) Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study. Leukemia 27(9):1874–1881
36. Finazzi G (2004) A prospective analysis of thrombotic events in the European collaboration study on low-dose aspirin in polycythemia (ECLAP). Pathol Biol (Paris) 52:285–288
37. Landolfi R, Marchioli R, Kutti J, Gisslinger H, Tognoni G, Patrono C, Barbui T (2004) Efficacy and safety of low-dose aspirin in polycythemia vera. N Engl J Med 350(2):114–124
38. Kiladjian JJ, Cassinat B, Chevret S, Turlure P, Cambier N, Roussel M, Bellucci S, Grandchamp B, Chomienne C, Fenaux P (2008) Pegylated interferon-alfa-2a induces complete hematologic molecular responses with low toxicity in polycythemia vera. Blood 112 (8):3065–3072
39. Gisslinger H, Zagrijtschuk O, Veronika B-A, Thaler J, Schloegl E, Guenther A. Gastl, Wolf D, Kralovics R, Gisslinger B, Strecker K, Egle A, Melchardt T, Burgstaller S, Willenbacher E, Schalling M, Nicole C. Them, Kadlecova P, Klade C, Greil R (2017) Ropeginterferon Alfa-2b Induces high rates of clinical, hematological and molecular responses in polycythemia vera: two-year results from the first prospective randomized control trial. In: The 59th annual meeting & exposition of the American Society of Hematology, Atlanta, GA, 9–12 Dec 2017. (Abstract nr 320)
40. Vannucchi AM (2015) Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med 372(5):426–435
41. Alvarez-Larrán A, Pereira A, Guglielmelli P, Hernández-Boluda JC, Arellano-Rodrigo E, Ferrer-Marín F, Samah A, Griesshammer M, Kerguelen A, Andreasson B, Burgaleta C, Schwarz J, García-Gutiérrez V, Ayala R, Barba P, Gómez-Casares MT, Paoli C, Drexler B, Zweegman S, McMullin MF, Samuelsson J, Harrison C, Cervantes F, Vannucchi AM, Besses C (2016) Antiplatelet therapy versus observation in low-risk essential thrombocythemia with a CALR mutation. Haematologica 101(8):926–931
42. Alvarez-Larran et al (2010) Observation versus antiplatelet therapy as primary prophylaxis for thrombosis in low-risk essential thrombocythemia. Blood 116(8):1205–1210
43. Chu DK, Hillis CM, Leong DP, Anand SS, Siegal DM (2017) Benefits and risks of antithrombotic therapy in essential thrombocythemia. Ann Intern Med 167:170–180
44. Cortelazzo S, Finazzi G, Ruggeri M, Vestri O, Galli M, Rodeghiero F, Barbui T (1995) Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. N Engl J Med 332(17):1132–1136
45. Harrison CN, Campbell PJ, Buck G, Wheatley K, East CL, Bareford D, Wilkins BS, van der Walt JD, Reilly JT, Grigg AP, Revell P, Woodcock BE, Green AR (2005) Hydroxyurea compared with anagrelide in high-risk ET. N Engl J Med 353(1):33–45
46. Gisslinger H, Gotic M, Holowiecki J, Penka M, Thiele J, Kvasnicka HM, Kralovics R (2013) Anagrelide compared with hydroxyurea in WHO-classified essential thrombocythemia: the ANAHYDRET study, a randomized control trial. Blood 121(10):1720–1728
47. Harrison CN, Mead AJ, Panchal A, Fox S, Yap C, Gbandi E, Houlton A, Alimam S, Ewing J, Wood M, Chen F, Coppell J, Panoskaltsis N, Knapper S, Ali S, Hamblin A, Scherber R, Dueck AC, Cross NCP, Mesa R, McMullin MF (2017) Ruxolitinib vs best available therapy for ET intolerant or resistant to hydroxycarbamide. Blood 130(17):1889–1897
48. Ellis MH, Lavi N, Vannucchi A, Harrison C (2014) Treatment of thromboembolic events coincident with the diagnosis of myeloproliferative neoplasms: a physician survey. Thromb Res 134:251–254
49. Ianotto et al (2017) Administration of direct oral anticoagulants in patients with myeloproliferative neoplasms. Int J Hematol 106:517–521
50. Boddu P, Falchi L, Hosing C, Newberry K, Bose P, Verstovsek S (2017) The role of thrombocytapheresis in the contemporary management of hyperthrombocytosis in myeloproliferative neoplasms: a case-based review. Leuk Res 58:14–22

51. Adami R (1993) Therapeutic thrombocytapheresis: a review of 132 patients. Int J Artif Organs 16(Suppl. 5):183–184
52. Ruggeri M, Rodeghiero F, Tosetto A, Castaman G, Scognamiglio F, Finazzi G, Delaini F, Micò C, Vannucchi AM, Antonioli E, De Stefano V, Za T, Gugliotta L, Tieghi A, Mazzucconi MG, Santoro C, Barbui T (2008) Postsurgery outcomes in patients with polycythemia vera and essential thrombocythemia: a retrospective survey. Blood 111:666–671

Anticoagulation in the Setting of Primary and Metastatic Brain Tumors

12

Charlene Mantia and Jeffrey I. Zwicker

Contents

C. Mantia
Division of Hematology and Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA
e-mail: cmantia@bidmc.harvard.edu

J. I. Zwicker (✉)
Division of Hemostasis and Thrombosis, Division of Hematology and Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, USA
e-mail: jzwicker@bidmc.harvard.edu

G. Soff (ed.), *Thrombosis and Hemostasis in Cancer*, Cancer Treatment and Research 179, https://doi.org/10.1007/978-3-030-20315-3_12

12.1 Brain Tumors

Primary and secondary brain tumors represent a diverse group of neoplasms. There were 23,800 new cases of primary brain neoplasms in the USA in 2017 [1]. The incidence of secondary brain tumors from metastatic disease is not as well-known but represents the most frequent type of brain tumor in adults. It is estimated that one-fourth of patients with cancer will develop an intracranial metastasis [2]. The incidence of metastatic brain tumors has been increasing which is thought to be the result of improved diagnosis with more sensitive imaging techniques, longer survival of patients with cancer due to more effective treatment options, and an older patient population overall [2]. As the population of patients living with brain tumors increases, so does the frequency of inherent complications such as venous thromboembolism (VTE) and intracranial hemorrhage.

12.2 Incidence and Pathophysiology of Venous Thromboembolism

Patients with brain tumors frequently develop VTE. It is estimated that patients with primary and secondary brain tumors have one of the highest rates of VTE seen in patients with cancer. About 20% of patients with metastatic brain tumors will be diagnosed with a VTE [3]. In patients with glioma, the most common type of primary brain tumor, VTE is estimated to occur in upwards of 30% of patients [4].

There are direct and indirect factors contributing to hypercoagulability in patients with brain tumors. The tumors themselves are known to release procoagulant factors into circulation. For example, patients with glioma have elevated levels of tissue factor, which is a transmembrane receptor that binds factor VII/VIIa to initiate coagulation in vivo. Tumors that express high levels of tissue factor are associated with increased rates of VTE when compared with tumors that express lower levels of tissue factor [5–8]. Tumor cells release tissue factor-bearing microparticles into circulation and high levels of these procoagulant microparticles are associated with an increased risk of VTE and shortened overall survival [5, 6, 9–17]. Tissue factor is commonly over-expressed in glioma and expression levels are linked to histologic grade [18]. In fact, labeled tissue factor antibodies are currently being evaluated by single-photon emission computed tomography to radiologically assess glioma tumor grade [19]. Increased circulating microparticles have similarly been demonstrated in glioma patients diagnosed with a VTE relative those without VTE [15].

Platelet activation has increasingly been implicated as playing a central role in cancer-associated thrombosis with platelet activation occurring by a number of potential mechanisms including neutrophil extracellular traps (NETs) interaction and podoplanin secretion. Neutrophils are found in the tumor microenvironment and can release extracellular DNA traps called NETs which activate platelets, causing aggregation and thrombosis [20]. While there is limited data on NETs as

mediating thrombosis in patients with brain tumors, circulating tumor-derived microparticles have been shown to interact with NETs and augment thrombus formation in animal models of cancer-associated thrombosis [21]. Gliomas also express the glycoprotein podoplanin, which can induce platelet activation through the CLEC2 receptor. Increased levels of podoplanin expression in tumor cells have been shown to be associated with increased D-dimer levels, lower platelet counts and the development of VTE suggesting a potential contributing role in the development of thrombosis [22, 23]. Beyond the tumor microenvironment, patients with brain tumors commonly have additional factors that can increase risk of VTE such as neurosurgery, chemotherapy, and decreased mobility.

12.3 Incidence and Pathophysiology of Intracranial Hemorrhage

Spontaneous intracranial hemorrhage is a common complication in patients with primary and secondary brain tumors. The incidence of intracranial hemorrhage varies between studies based on the definition of intracranial hemorrhage used, method used to identify cases, and types of malignancy. The definition of intracranial hemorrhage can range from asymptomatic hemosiderin deposition within tumors noted on routine imaging to large bleeds with associated edema causing clinical symptoms [4]. The cumulative incidence of intracranial hemorrhage in primary brain tumors is estimated at 30% at 1 year [24]. Rates of intracranial hemorrhage for patients with intracranial metastases are considered lower (approximately 20% at 1 year) but the rates vary widely according to tumor type [25]. Renal cell carcinoma and melanoma are considered tumors with the highest rates of intracranial hemorrhage with rates of hemorrhage approaching 50% [25].

For patients with primary brain tumors or metastatic solid tumors to the brain, the majority of hemorrhages occur at the site of the tumor. In a study of 208 cancer patients who suffered from spontaneous intracranial hemorrhage at Memorial Sloan-Kettering Cancer Center between 2000 and 2007, 87% had cerebral hemorrhage and a smaller percentage of patients had subarachnoid hemorrhage or intraventricular hemorrhage [26]. Approximately, two-thirds of all hemorrhages occurred within the tumor. Less than one-half of patients had evidence of coagulopathy at the time of hemorrhage. The vast majority of patients in this study were identified because they were symptomatic (94%) with hemiparesis, headache, impaired consciousness, or seizure [26].

The pathophysiology of hemorrhage into a primary or secondary brain tumor is not fully understood but is thought to be due to the instability of newly formed blood vessels. Vascular endothelial growth factor (VEGF) is expressed by tumor cells to stimulate neovascularization and tumor growth. These new blood vessels have been shown to be fragile and permeable [27]. Several studies have suggested an association between the level of VEGF expression and intratumoral hemorrhage [28–30]. Tumor cells also secrete enzymes called matrix metalloproteinases

(MMPs) that degrade extracellular matrix proteins, allowing tumor cells to invade surrounding tissue and spread [30]. Destruction of the matrix surrounding blood vessels can lead to instability and rupture. Patients with aneurysms have been found to have higher levels of MMPs in the vasculature [31]. In a study of patients with metastatic brain tumors, higher levels of VEGF and MMPs were seen in the pathological specimens of brain tumors with hemorrhage compared to tumors without hemorrhage [30]. These studies suggest that VEGF and MMPs expressed by tumors may contribute to spontaneous intracranial hemorrhage.

Clinical outcomes following spontaneous intracranial hemorrhage in patients with brain tumors are poor. Patients are more likely to experience symptoms from an intracranial hemorrhage than from other cerebrovascular events such as ischemic stroke. In one study, among the patients who were hospitalized with intracranial hemorrhage and survived to hospital discharge, only 15% were completely independent while 63% were partially or completely dependent on others for their care [26]. Overall survival is short for patients with malignancy who experience an intracranial hemorrhage. One month after intracranial hemorrhage, mortality exceeds 30% and at one year the mortality rate is over 75% [26]. The outcomes following intracranial hemorrhage are in large part dictated by initial presentation and poor overall prognosis of brain tumors. Predictors of poor outcome and increased mortality rates include multiple areas of hemorrhage, treatment for intracranial hypertension, metastatic solid tumor or hematologic central nervous system neoplasms, active chemotherapy treatment, and clinical hemiparesis [26].

12.4 Anticoagulation in the Setting of Metastatic Brain Tumors

VTE is a serious complication in patients with malignancy and represents one of the leading causes of death [32]. Anticoagulation is considered standard of care to treat VTE in cancer patients in order to minimize morbidity and mortality; however, there is often hesitancy to start patients with brain tumors on anticoagulation given the concern for intracranial hemorrhage.

Despite the high rates of hemorrhage in patients with secondary brain tumors, there is increasing evidence to support the safety of therapeutic anticoagulants. One of the first studies to evaluate the use of anticoagulation in patients with brain metastases by Schiff et al. reviewed outcomes of 51 patients who were treated for VTE between 1980 and 1992 [33]. In this study, 42 patients received varying doses of anticoagulation with heparin or warfarin. There were three cases (7%) of intracranial hemorrhage associated with significant morbidity and mortality as well as three cases (7%) of clinically silent intracranial hemorrhage. Two of the patients who died from intracranial hemorrhage demonstrated supratherapeutic levels of anticoagulation. The other nine study patients were either not treated or had an inferior vena cava (IVC) filter placed with high rates of VTE recurrence. The

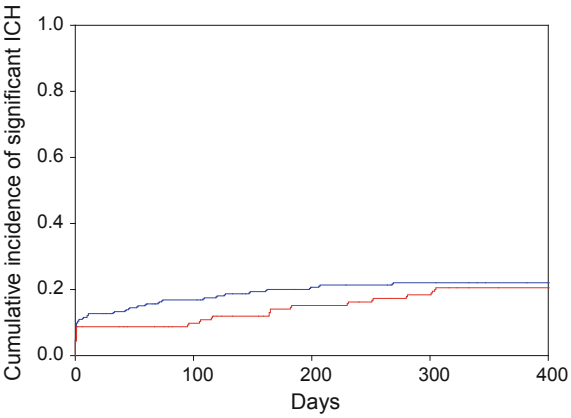

Fig. 12.1 No difference in the rate of major intracranial hemorrhage with anticoagulation in brain metastases. One-year cumulative incidence of major intracranial hemorrhage with enoxaparin (red) was 21% versus 22% without anticoagulation (blue), (Gray test $P = 0.87$) [25]

authors concluded that anticoagulation was effective at preventing recurrent VTE and was considered safe in patients with brain metastases [33].

More recent studies have also concluded that anticoagulation does not confer an increased risk of intracranial hemorrhage in patients with solid tumor malignancies metastatic to the brain. Our group performed a matched, retrospective cohort study of 293 patients with cancer and brain metastases [25]. Outcomes of patients with VTE who received therapeutic enoxaparin were compared to controls with brain metastases who were matched for age, sex, diagnosis, and date of treatment. All radiologic imaging with evidence of hemorrhage was re-reviewed in a blinded manner, and the size of hemorrhages was calculated. We did not observe a statistical difference in the incidence of major intracranial hemorrhage in patients treated for venous thromboembolism with enoxaparin compared with patients not on anticoagulation (Fig. 12.1). The cumulative incidence of significant intracranial hemorrhage (defined as greater than 10 mL in volume, symptomatic or requiring surgical intervention) occurred in 21% in patients on enoxaparin and 22% in patients who were not on anticoagulation. These results are consistent with several other smaller studies that did not identify an increased risk of intracranial hemorrhage with anticoagulation. In our meta-analysis of nine retrospective cohort studies, there was no statistically significant increase in the odds ratio for intracranial hemorrhage in patients with brain metastases treated with therapeutic anticoagulation (OR 1.07; 95% CI, 0.61–1.88) [34].

Rates of spontaneous intracranial hemorrhage vary based on the type of malignancy, and there is less data regarding the safety of anticoagulation in those tumors considered greatest risk for hemorrhage such as renal cell carcinoma or

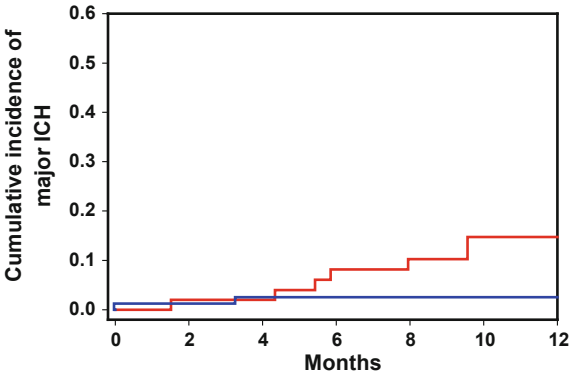

Fig. 12.2 Higher rate of major intracranial hemorrhage in glioma patients on anticoagulation. One-year cumulative incidence of major intracranial hemorrhage was 14.7% with enoxaparin (red) and 2.5% without anticoagulation (blue), (P = 0.036) [24]

melanoma. We observed approximately 50% of the 60 patients with renal cell carcinoma or melanoma had evidence of any intracranial hemorrhage ranging in size from trace to significant [25]. Among patients with renal cell carcinoma or melanoma on enoxaparin for treatment of VTE, 35% experienced a significant intracranial hemorrhage which was similar to the 34% of patients who were not on anticoagulation (P = 0.88) [25]. Another study of 74 patients with brain metastases from melanoma did not find any increased risk of intracranial hemorrhage for patients on anticoagulation compared with those who were not [35]. More data on specific tumor types at highest risk of intracranial hemorrhage is needed before we can definitively establish the safety of therapeutic anticoagulation in these populations.

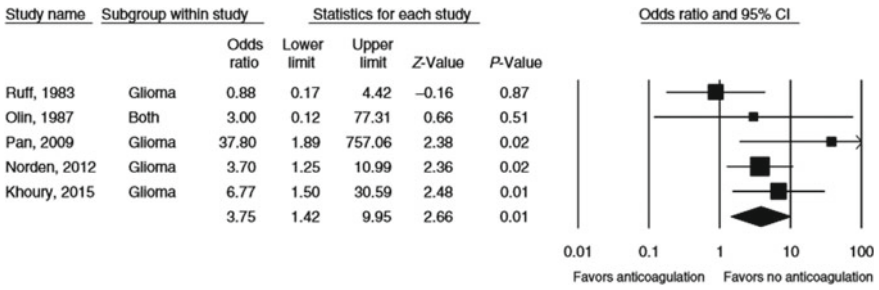

Fig. 12.3 Forest plot and pooled estimate of odds ratio of intracranial hemorrhage in patients with glioma on anticoagulation [34]

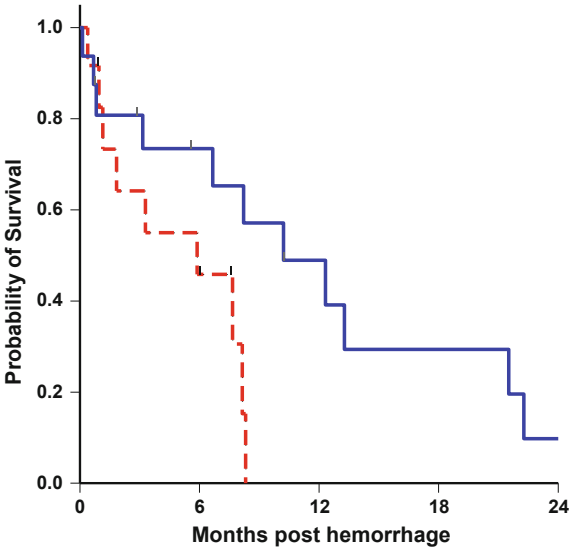

Fig. 12.4 Overall survival following intracranial hemorrhage in glioma influenced by anticoagulation status. Overall survival following hemorrhage was significantly shorter in the enoxaparin cohort (red) versus controls (blue) (3.3 vs. 10.2 months, respectively, log-rank $p = 0.012$) [24]

12.5 Anticoagulation in the Setting of Primary Brain Tumors

Studies evaluating the safety of anticoagulation in patients with primary brain tumors have reported varying results. An older, retrospective study by Choucair et al. reviewed the cases of 36 patients with glioma, the most common type of primary brain tumor, who developed VTE from 1977 to 1986 [36]. Of the 22 patients who were treated with anticoagulation for at least 3 months, none experienced an intracranial hemorrhage. In a more recent retrospective study of 64 patients who were diagnosed with VTE, 36 were treated with anticoagulation and 3 patients (8.3%) suffered an intracranial hemorrhage [37].

We recently published intracranial hemorrhage outcomes among 133 patients with glioma [24]. In a matched, retrospective cohort study with blinded radiology review, the risk of a major intracranial hemorrhage was greater than 3-fold higher in the patients who received anticoagulation with enoxaparin compared with those patients who did not receive anticoagulation (Fig. 12.2). During the time of exposure to enoxaparin, there was more than a 13-fold increased risk of developing a major intracranial hemorrhage (HR 13.29; 95% CI, 3.33–52.85; $P < 0.0001$). These results are similar to the conclusions of a meta-analysis that included five studies [34]. Therapeutic anticoagulation in glioma was associated with a significant increase in intracranial hemorrhage with a pooled odds ratio of 3.75 (95% CI, 1.42–9.95) (Fig. 12.3).

Clinical outcomes are poor in patients with primary brain tumors who suffer an intracranial hemorrhage while on anticoagulation. We observed that the median survival following the diagnosis of intracranial hemorrhage while on enoxaparin

was 3.3 months compared with 10.2 months for patients who had an intracranial hemorrhage and were not on anticoagulation [24] (Fig. 12.4).

12.6 Alternative Treatments for VTE in Patients with Brain Tumors

Although there appears to be an increased risk of intracranial hemorrhage in patients with primary brain tumors treated with anticoagulation, it is not known whether outcomes are better with alternative treatments. Other management options include placement of an IVC filter, reduced-intensity anticoagulation, direct oral anticoagulants (DOACs), or conservative management without intervention. A retrospective cohort study analyzed outcomes of 145 patients with glioblastoma and VTE at the Cleveland Clinic from 2007 to 2013 [38]. Interestingly, the relative distribution of no treatment, IVC filter placement alone, and therapeutic enoxaparin were roughly similar (approximately 25% each) with another 15% receiving anticoagulation in combination with IVC filter placement. Of all the patients who had IVC filters placed, 30% suffered a recurrent VTE and 5% required filter removal due to mechanical complications which highlights the potential disadvantages of IVC filter placement in a highly thrombotic population.

There is limited data available on the safety of DOACs for the treatment of VTE in patients with brain tumors. In a randomized trial of edoxaban versus dalteparin for the treatment of cancer-associated thrombosis, edoxaban was noninferior to dalteparin for the composite endpoint for recurrent VTE and major hemorrhage [38]. Among the 74 patients in this study with brain tumors, the rates of recurrent VTE and major hemorrhages were similar with edoxaban and dalteparin (19.4 vs.

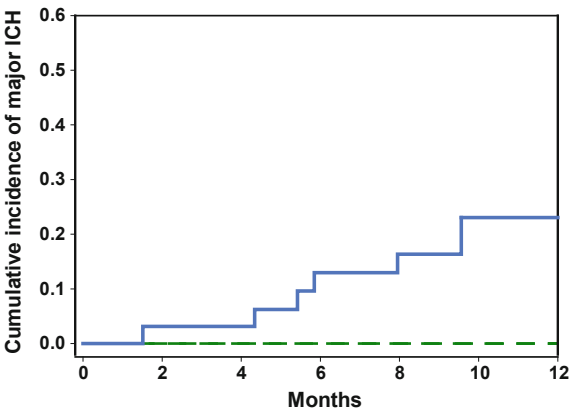

Fig. 12.5 PANWARDS score predicts a higher likelihood of major intracranial hemorrhage on anticoagulation in glioma. The cumulative incidence of major intracranial hemorrhage at 1 year in glioma patients receiving anticoagulation with scores ≥ 25 (blue) was 23% (95% CI, 9.91–39.41) compared with 0% for lower scores (green, $P = 0.03$) [24]

18.6%, respectively, $p = 0.68$). Only two of these patients with brain tumors receiving edoxaban and four receiving dalteparin suffered a major hemorrhage but the location and specifics of the major bleeds were not described [39].

At the present time, the decision to use anticoagulation is individualized based on a specific patient's perceived risk of recurrent clotting versus bleeding. A number of hemorrhage prediction tools have been developed and validated for therapeutic anticoagulation in atrial fibrillation. However, these models are skewed to predict the more common gastrointestinal hemorrhages. Hankey et al. reported a model that was developed to predict intracranial hemorrhage in patients with atrial fibrillation on anticoagulation [40]. This scoring system called PANWARDS uses risk factors such as low platelet count, low albumin, no history of congestive heart failure, use of warfarin as anticoagulant, older age, race, hypertension, and history of stroke or transient ischemic attack to estimate the risk of intracranial hemorrhage. We applied the risk score to patients in glioma and it appears to accurately predict a cohort of patients who are unlikely to bleed on therapeutic anticoagulation [24]. There were no cases of major intracranial hemorrhage in patients with a PANWARDS score of less than 25 (sensitivity of 100%, specificity of 40%) (Fig. 12.5).

12.7 Summary

Venous thromboembolism and intracranial hemorrhage are common complications in the setting of primary and secondary brain tumors. In patients with brain metastases, low molecular heparin does not increase the rates of intracranial hemorrhage. In light of the current evidence suggesting an increased rate of intracranial hemorrhage in patients with glioma, judicial use of therapeutic anticoagulation is warranted. We advise a careful consideration of risk factors for hemorrhage in glioma. Until more data becomes available, it is reasonable to consider full dose anticoagulation with careful monitoring or alternative strategies that may include dose-modification of anticoagulants and/or placement of IVC filters in those patients at greatest risk for hemorrhage.

References

1. SEER Cancer Stat Facts: Brain and Other Nervous System Cancer. National Cancer Institute. Bethesda, MD. https://seer.cancer.gov/statfacts/html/brain.html
2. Fox BD, Cheung VJ, Patel AJ, Suki D, Rao G (2011) Epidemiology of metastatic brain tumors. Neurosurg Clin N Am 22(1):1–6
3. Gerber DE, Grossman SA, Streiff MB (2006) Management of venous thromboembolism in patients with primary and metastatic brain tumors. J Clin Oncol 24(8):1310–1318
4. Weinstock MJ, Uhlmann EJ, Zwicker JI (2016) Intracranial hemorrhage in cancer patients treated with anticoagulation. Thromb Res 140(Suppl 1):S60–S65
5. Khorana AA, Francis CW, Menzies KE, Wang JG, Hyrien O, Hathcock J (2008) Plasma tissue factor may be predictive of venous thromboembolism in pancreatic cancer. J Thromb Haemost 6

6. Khorana AA, Ahrendt SA, Ryan CK, Francis CW, Hruban RH, Hu YC et al (2007) Tissue factor expression, angiogenesis, and thrombosis in pancreatic cancer. Clin Cancer Res 13(10): 2870–2875
7. Uno K, Homma S, Satoh T, Nakanishi K, Abe D, Matsumoto K et al (2007) Tissue factor expression as a possible determinant of thromboembolism in ovarian cancer. Br J Cancer 96(2):290–295
8. Abu Saadeh F, Norris L, O'Toole S, Mohamed BM, Langhe R, O'Leary J et al (2013) Tumour expresion of tissue factor and tissue factor pathway inhibitor in ovarian cancer-relationship with venous thrombosis risk. Thromb Res 132(5):627–634
9. Bharthuar A, Khorana AA, Hutson A, Wang J-G, Key NS, Mackman N et al (2013) Circulating microparticle tissue factor, thromboembolism and survival in pancreaticobiliary cancers. Thrombosis Res 132(2):180–184
10. Tesselaar ME, Romijn FP, Linden IK, Bertina RM, Osanto S (2009) Microparticle-associated tissue factor activity in cancer patients with and without thrombosis. J Thromb Haemost 7
11. Hron G, Kollars M, Weber H, Sagaster V, Quehenberger P, Eichinger S et al (2007) Tissue factor-positive microparticles: cellular origin and association with coagulation activation in patients with colorectal cancer. Thromb Haemost 97(1):119–123
12. Manly DA, Wang J, Glover SL, Kasthuri R, Liebman HA, Key NS et al (2010) Increased microparticle tissue factor activity in cancer patients with Venous Thromboembolism. Thromb Res 125(6):511–512
13. Campello E, Spiezia L, Radu CM, Bulato C, Castelli M, Gavasso S et al (2011) Endothelial, platelet, and tissue factor-bearing microparticles in cancer patients with and without venous thromboembolism. Thromb Res 127
14. Bharthuar A, Khorana AA, Hutson A, Wang JG, Key NS, Mackman N et al (2013) Circulating microparticle tissue factor, thromboembolism and survival in pancreaticobiliary cancers. Thromb Res 132
15. Sartori MT, Della Puppa A, Ballin A, Campello E, Radu CM, Saggiorato G et al (2013) Circulating microparticles of glial origin and tissue factor bearing in high-grade glioma: a potential prothrombotic role. Thromb Haemost 110(2):378–385
16. Zwicker JI, Liebman HA, Bauer KA, Caughey T, Campigotto F, Rosovsky R et al (2013) Prediction and prevention of thromboembolic events with enoxaparin in cancer patients with elevated tissue factor-bearing microparticles: a randomized-controlled phase II trial (the Microtec study). Br J Haematol 160(4):530–537
17. Zwicker JI, Liebman HA, Neuberg D, Lacroix R, Bauer KA, Furie BC et al (2009) Tumor-derived tissue factor-bearing microparticles are associated with venous thromboembolic events in malignancy. Clin Cancer Res 15(22):6830–6840
18. Hamada K, Kuratsu J, Saitoh Y, Takeshima H, Nishi T, Ushio Y (1996) Expression of tissue factor correlates with grade of malignancy in human glioma. Cancer 77(9):1877–1883
19. Takashima H, Tsuji AB, Saga T, Yasunaga M, Koga Y, Kuroda JI et al (2017) Molecular imaging using an anti-human tissue factor monoclonal antibody in an orthotopic glioma xenograft model. Sci Rep 7(1):12341
20. Demers M, Krause DS, Schatzberg D, Martinod K, Voorhees JR, Fuchs TA et al (2012) Cancers predispose neutrophils to release extracellular DNA traps that contribute to cancer-associated thrombosis. Proc Natl Acad Sci U S A 109(32):13076–13081
21. Leal AC, Mizurini DM, Gomes T, Rochael NC, Saraiva EM, Dias MS et al (2017) Tumor-derived exosomes induce the formation of neutrophil extracellular traps: implications for the establishment of cancer-associated thrombosis. Sci Rep 7:6438
22. Mir Seyed Nazari P, Riedl J, Preusser M, Posch F, Thaler J, Marosi C et al (2018) Combination of isocitrate dehydrogenase 1 (IDH1) mutation and podoplanin expression in brain tumors identifies patients at high or low risk of venous thromboembolism. J Thromb Haemost 16(6):1121−1127
23. Riedl J, Preusser M, Nazari PM, Posch F, Panzer S, Marosi C et al (2017) Podoplanin expression in primary brain tumors induces platelet aggregation and increases risk of venous thromboembolism. Blood 129(13):1831–1839

24. Mantia C, Uhlmann EJ, Puligandla M, Weber GM, Neuberg D, Zwicker JI (2017) Predicting the higher rate of intracranial hemorrhage in glioma patients receiving therapeutic enoxaparin. Blood 129(25):3379–3385
25. Donato J, Campigotto F, Uhlmann EJ, Coletti E, Neuberg D, Zwicker J (2015) Intracranial hemorrhage in patients with brain metastases treated with therapeutic enoxaparin: a matched cohort study. Blood 126(4):494–499
26. Navi BB, Reichman JS, Berlin D, Reiner AS, Panageas KS, Segal AZ et al (2010) Intracerebral and subarachnoid hemorrhage in patients with cancer. Neurology. 74(6):494–501
27. Cao R, Eriksson A, Kubo H, Alitalo K, Cao Y, Thyberg J (2004) Comparative evaluation of FGF-2-, VEGF-A-, and VEGF-C-induced angiogenesis, lymphangiogenesis, vascular fenestrations, and permeability. Circ Res 94(5):664–670
28. Jin Kim Y, Hyun Kim C, Hwan Cheong J, Min Kim J (2011) Relationship between expression of vascular endothelial growth factor and intratumoral hemorrhage in human pituitary adenomas. Tumori. 97(5):639–646
29. Cheng SY, Nagane M, Huang HS, Cavenee WK (1997) Intracerebral tumor-associated hemorrhage caused by overexpression of the vascular endothelial growth factor isoforms VEGF121 and VEGF165 but not VEGF189. Proc Natl Acad Sci U S A 94(22):12081–12087
30. Jung S, Moon KS, Jung TY, Kim IY, Lee YH, Rhu HH et al (2006) Possible pathophysiological role of vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs) in metastatic brain tumor-associated intracerebral hemorrhage. J Neurooncol 76(3):257–263
31. Goodall S, Crowther M, Hemingway DM, Bell PR, Thompson MM (2001) Ubiquitous elevation of matrix metalloproteinase-2 expression in the vasculature of patients with abdominal aneurysms. Circulation 104(3):304–309
32. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH (2007) Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost 5(3):632–634
33. Schiff D, DeAngelis LM (1994) Therapy of venous thromboembolism in patients with brain metastases. Cancer 73(2):493–498
34. Zwicker JI, Karp RL, Carrier M (2016) A meta-analysis of intracranial hemorrhage in patients with brain tumors receiving therapeutic anticoagulation. J Thromb Haemost 4(9):1736–1740
35. Alvarado G, Noor R, Bassett R, Papadopoulos NE, Kim KB, Hwu WJ et al (2012) Risk of intracranial hemorrhage with anticoagulation therapy in melanoma patients with brain metastases. Melanoma Res 22(4):310–315
36. Choucair AK, Silver P, Levin VA (1987) Risk of intracranial hemorrhage in glioma patients receiving anticoagulant therapy for venous thromboembolism. J Neurosurg 66(3):357–358
37. Yust-Katz S, Mandel JJ, Wu J, Yuan Y, Webre C, Pawar TA et al (2015) Venous thromboembolism (VTE) and glioblastoma. J Neurooncol 124(1):87–94
38. Edwin NC, Khoury MN, Sohal D, McCrae KR, Ahluwalia MS, Khorana AA (2016) Recurrent venous thromboembolism in glioblastoma. Thromb Res 137:184–188
39. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D et al (2018) Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 378(7): 615–624
40. Hankey GJ, Stevens SR, Piccini JP, Lokhnygina Y, Mahaffey KW, Halperin JL et al (2014) Intracranial hemorrhage among patients with atrial fibrillation anticoagulated with warfarin or rivaroxaban. The rivaroxaban once daily, oral, direct factor Xa inhibition compared with Vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation. Stroke 45(5):1304–1312

Bleeding Disorders Associated with Cancer

13

Simon Mantha

Contents

13.1 Introduction

Human neoplasms encompass a wide range of organ systems and manifestations, and alterations of hemostasis are commonly encountered in the oncology setting. Cancer-associated thrombosis is well described and the subject of much active research, but bleeding disorders secondary to malignancy are also clinically important and can be at times challenging for the treating physician. The mecha-

S. Mantha (✉)
Department of Medicine, Hematology Service, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA
e-mail: manthas@mskcc.org

G. Soff (ed.), *Thrombosis and Hemostasis in Cancer*, Cancer Treatment and Research 179, https://doi.org/10.1007/978-3-030-20315-3_13

nisms underlying alterations of hemostasis in cancer are diverse and can be related to both direct disease effect and treatment. Chemotherapy-induced thrombocytopenia is arguably the most common risk factor for bleeding in the cancer patient and is discussed in a separate chapter.

13.1.1 Acute Promyelocytic Leukemia

Acute promyelocytic leukemia (APL) is an uncommon myeloid neoplasm characterized by the t(15;17) genetic translocation and associated with a distinct coagulopathy resulting in a substantial risk of lethal bleeding during induction chemotherapy, estimated at about 5% of patients with modern treatment modalities [1–3].

The main coagulation abnormality seems to be a primary hyperfibrinolytic state mediated by the presence of Annexin II at the surface of malignant leukocytes [4, 5]. Annexin II catalyzes the activation of tissue plasminogen activator (TPA), which in turns cleaves plasminogen to the primary fibrinolytic enzyme plasmin [6]. Plasmin generated by this reaction will then lead to fibrinolysis and fibrinogenolysis. Another, less important mechanism at play in the coagulopathy of APL is disseminated intravascular coagulation triggered by tissue factor (TF) which is present in the leukemic blasts [7, 8]. TF is responsible for the activation of factor VII. The TF:factor VIIa complex will activate factor X and cause subsequent consumption of platelets, fibrinogen and other coagulation factors, further worsening the hemorrhagic diathesis [9].

Clinical manifestations of this coagulopathy can be of variable severity, ranging from mild mucocutaneous bleeding to hemorrhagic death [3]. Epistaxis, bruising, gastrointestinal (GI) or genitourinary bleeding, or bleeding at indwelling vascular catheter sites are all common. Hemostatic parameters are usually abnormal. The activated partial thromboplastin time (APTT) and prothrombin time (PT) tend to be prolonged and the fibrinogen level is typically depressed, while the platelet count is almost always decreased [10, 11]. Hemorrhagic mortality is usually secondary to intracranial or pulmonary bleeding.

The cornerstone of APL treatment consists of prompt administration of all-trans retinoic acid (ATRA) as soon as the diagnosis of APL is suspected [12]. ATRA has been demonstrated to cause differentiation of APL blasts, which leads to decreased production of TF and Annexin II, thus improving the coagulopathy [8, 13]. Aggressive blood product administration is also recommended during induction chemotherapy for APL, with a usual goal platelet count above 30,000–50,000/mcL and a desired fibrinogen above 100–150 mg/dL [12].

The main predictor of hemorrhagic death during induction chemotherapy for APL remains the total white blood cell count [14, 15]. Values above 10,000–

20,000/mcL signal a higher probability of dying from bleeding in the first 30 days after starting treatment. Unfortunately, there is still no specific intervention demonstrated to be useful in mitigating the coagulopathy for this high-risk strata.

13.1.2 Disseminated Intravascular Coagulation in Cancer

Disseminated intravascular coagulation (DIC) is commonly encountered in the cancer setting and may be acute, associated with hemorrhage, or chronic, associated with thrombosis [16]. Exposure of TF to the intravascular space is usually the primary mechanism leading to this consumptive coagulopathy, and the basis of management remains to treat the precipitating condition. Outside of APL, acute DIC related to cancer is found on occasion in other acute leukemias [17, 18]. In most cases of clinically significant acute DIC, the APTT is prolonged and the platelet count is decreased. Fibrinogen is an acute phase reactant and will not always be decreased in early acute DIC. However, most instances of DIC in cancer are chronic and do not lead to exhaustion of coagulation factor levels and bleeding due to compensation through increased synthesis by the liver. Chronic DIC is commonly encountered in patients with solid tumors and is associated with an increased risk of thrombosis, secondarily to enhanced fibrin production.

DIC in non-M3 (i.e., non-APL) AML can lead to bleeding manifestations; however, typically other factors also contribute to the risk of such events, including thrombocytopenia secondary to administration of cytotoxic chemotherapy [19]. TF is thought to play a role in thrombin activation and exhaustion of coagulation factor reserves; however, this process has not been fully elucidated. The cornerstone of treatment for acute DIC secondary to non-M3 AML remains to replete platelets, fibrinogen and other coagulation factors with blood products, along with cytoreduction [20]. Recombinant soluble thrombomodulin is being explored as another therapeutic avenue [21, 22].

13.1.3 Acquired Hemophilia

Acquired hemophilia is an autoimmune disorder characterized by the production of an antibody against coagulation factor VIII. This antibody is usually directed against a phospholipid binding site of the enzyme and acts as an inhibitor [23]. Factor VIII activity in affected patients will often be markedly decreased or absent (<1%) [24]. The APTT will be prolonged.

The APTT mixing study of 1:1 patient:normal plasma will show prolongation, particularly with 37 C incubation [25]. As antibody binding to the factor VIII antigen in the normal plasma is time-dependent, sometimes the APTT mixing study will be normal or minimally prolonged at the immediate time-point. However, with incubation, the APTT will be prolonged [25].

Acquired hemophilia is very rare in the general population, with a yearly incidence of about 1.5/million and a median age at presentation of 78 years [24].

Patients tend to present with soft tissue hematomas, surgical, GI, genitourinary or other mucocutaneous bleeding [26]. In one large population study, about 15% of cases were associated with cancer [24]. Prostate cancer (25.3%), lymphoma (24.4%), chronic lymphocytic leukemia (22.3%), plasma cell dyscrasias (20.0%) and lung cancer (15.8%) were the most commonly associated neoplasms in a recent literature review [27].

There is no prospective trial dedicated to evaluating treatment modalities for acquired hemophilia occurring in the setting of cancer. Corticosteroids, cyclophosphamide, rituximab, prothrombin complex concentrate, recombinant activated factor VII, human factor VIII (recombinant or plasma-derived) and recombinant porcine factor VIII have all been used with an overall complete response rate of 62.1% in the oncology setting in one series. The best predictor of inhibitor response was successful treatment of the malignancy [27].

13.1.4 Acquired von Willebrand Disease

von Willebrand factor (VWF) is involved in the process of platelet adhesion to exposed subendothelium and protects coagulation factor VIII from proteolytic degradation in the peripheral blood. While inherited von Willebrand disease is by far more frequent, acquired forms have been described including cases mediated by cancer [28]. The two main categories of malignancy encountered in association with acquired von Willebrand disease (AVWD) are myeloproliferative and lymphoid neoplasms, reported in 15 and 48% of patients, respectively, in one international registry [29].

An elevated platelet count in the setting of a myeloproliferative neoplasm like essential thrombocythemia has been shown to increase the risk of AVWD, perhaps through adsorption of VWF multimers at the surface of platelets or the action of proteases [30–33]. Administration of a myelosuppressive agent like hydroxyurea typically helps mitigate bleeding symptoms, which usually consist of mucocutaneous bleeding (purpura, epistaxis, gingival bleeding, etc.). Laboratory evaluation is usually suggestive of the type 2A variant, with a decreased VWF activity, a preserved VWF antigen level and a relative decrease in high-molecular-weight VWF multimers on electrophoresis [33].

A broad range of lymphoid neoplasms have been associated with AVWD, including non-Hodgkin lymphoma, chronic lymphocytic leukemia, multiple myeloma, Waldenström's macroglobulinemia (WM) and monoclonal gammopathy of unknown significance (MGUS) [34, 35]. Several mechanisms are potentially involved, including direct interference by a paraprotein, proteolytic cleavage of VWF and formation of auto-antibodies against VWF [36]. Bleeding tends to be mucocutaneous. Treatment of the primary neoplasm with chemotherapy has been shown to improve the bleeding diathesis in select cases.

AVWD has also been described in association with Wilm's tumor, the most common renal neoplasm in children. The exact mechanism is unclear, and this bleeding disorder might be multifactorial. A recent series of 186 patients with Wilm's tumor reported an incidence of 4.3% for AVWD [37]. The coagulation defect cleared in all cases following initiation of cancer-directed therapy.

13.1.5 Leukostasis

Leukostasis is a clinical syndrome characterized by occlusion of the microvasculature by malignant white cells, usually in the setting of acute myeloid leukemia and more rarely in the setting of acute lymphoblastic leukemia and other leukemias [38]. This syndrome is usually encountered only in patients with a myeloid blast count above 100,000/mcL, although it can occur at lower levels. The manifestations mostly consist of respiratory insufficiency and cerebral ischemia; however, sometimes bleeding can occur [39, 40]. The latter might be mediated by cytokines released by blasts or cell surface receptors interacting with the vascular wall. The main approach to treatment is cytoreduction with chemotherapy or leukapheresis.

13.1.6 Paraproteins and Hyperviscosity Syndrome

Paraproteins can be found in MGUS, multiple myeloma and WM. Bleeding is especially common in WM and was noted in 23% of patients at diagnosis in one series [41]. These clonal immunoglobulins have been associated with bleeding through several mechanisms, including interference with VWF (see above), platelet coating and hyperviscosity [42]. It is unclear how platelet coating mediates bleeding, but paraprotein specificity for GPIIIa has been demonstrated in one case [43]. It has also not been elucidated why hyperviscosity causes mucocutaneous bleeding. Hyperviscosity is a common phenomenon in WM, and long-term treatment is based on controlling the primary neoplasm with chemotherapy. In the short term, plasmapheresis is recommended for severe manifestations [44].

13.1.7 Amyloidosis

Amyloid light chain (AL) amyloidosis occurs secondarily to production of free immunoglobulin light chains by a plasma cell clone, often in the setting of multiple myeloma but also associated with MGUS and more rarely WM. Those free chains accumulate in tissues and lead to organ dysfunction. Bleeding manifestations are common and appear to be due to several mechanisms [45, 46].

The most common is a defect in small vessels secondary to amyloid infiltration, causing vascular wall fragility and impaired vasoconstriction following injury [47]. This usually manifests itself only by purpura and easy bruising; however, GI bleeding has been reported. The finding of periorbital purpura, or "raccoon eyes,"

has been well described in the setting of AL amyloidosis. No specific treatment is available, short of reducing the amount of amyloid deposits through chemotherapy.

A less common finding in AL amyloidosis is acquired coagulation factor X (FX) deficiency, as noted in 8.7% of patients in one series [48]. This occurs through adsorption of FX on amyloid deposits and eventual depletion of circulating factor levels, with ensuing bleeding manifestations [49, 50]. Clinical features include mucocutaneous bleeding (purpura, easy bruising, epistaxis), GI bleeding and impaired surgical hemostasis. Both the APTT and PT can be prolonged, with complete correction noted on mixing study. Infusion of exogenous FX by means of fresh frozen plasma or prothrombin complex concentrate has been used; however, the biological half-life of this factor will be reduced and administering sufficient amounts can be challenging [51]. Treatment with recombinant activated factor VII has been attempted in some cases in an attempt to circumvent this problem [52]. Splenectomy has been shown to alleviate the FX deficiency in select cases, potentially through removal of amyloid [53].

13.1.8 Platelet Aggregation Defects in Myeloid Malignancies

Myeloproliferative neoplasms are commonly accompanied by bleeding [54]. Essential thrombocythemia and polycythemia vera in particular have long been associated with mucocutaneous bleeding manifestations, including easy bruising and GI bleeding. This can be attributed to AVWD as discussed above, but there is also evidence of primary platelet dysfunction, with aggregation and secretion defects identified [55–57]. The exact mechanism is unclear, but this could arguably stem from abnormal gene expression mediated by clonal defects associated with the neoplasm. However, given the lack of correlation between platelet function assay results and overt bleeding manifestations, it is unclear at this point if intrinsic platelet defects contribute to the risk of bleeding beyond AVWD [58].

Myelodysplastic syndrome (MDS) has also been associated with platelet aggregation defects. Decreased aggregation has been reported for epinephrine, arachidonic acid, ADP, collagen and ristocetin in 75, 54, 46, 43 and 22% of patients in one review of the literature [59]. However, clinical bleeding in the absence of thrombocytopenia is uncommon so the significance of these laboratory abnormalities is unclear.

13.1.9 Drug Effects

Thrombocytopenia is by far the most common mechanism by which anti-neoplastic drugs have been known to cause bleeding; this is discussed in a dedicated chapter. Other types of drug-induced hemostatic impairment have been found to occur secondarily to vessel wall alterations from anti-vascular endothelial growth factor (VEGF) therapy and platelet dysfunction from ibrutinib.

Most of the evidence in regard to bleeding from anti-VEGF therapy comes from published experience with bevacizumab, an anti-VEGF monoclonal antibody. A meta-analysis of 20 randomized trials showed an incidence of 30.4% for any bleeding event, with grade ≥ 3 bleeding occurring in 3.5% of participants on bevacizumab [60]. The relative risk (RR) of any bleeding for bevacizumab versus control was 2.48 (95% CI = 1.93–3.18), with a dose effect noted. The increase in risk of high-grade bleeding for bevacizumab versus control was modest, with a RR of 1.91 (95% CI = 1.36–2.68). A less pronounced effect was noted with tyrosine kinase inhibitors (TKI's) of the VEGF receptor, of which several are approved for clinical use. A meta-analysis of 27 randomized trials of vandetanib, gefitinib, erlotinib, sunitinib, axitinib, sorafenib, pazopanib or regorafenib showed a risk of any bleeding event of 9.1% in the TKI group, compared with 1.3% for grade ≥ 3 bleeding. The RR of any bleeding event for TKI versus control was 1.67 (95% CI 1.19–2.33), but no significant difference was found for high-grade events [61]. There are also meta-analytic data evaluating the risk of bleeding on ramucirumab, a monoclonal antibody directed against the VEGF receptor. An analysis combining 6 randomized trials noted a RR of any bleeding of 2.0 (95% CI = 1.8–2.2) for ramucirumab versus control, but no significant difference in grade ≥ 3 events [62]. Lastly, substantially less data on bleeding complications are available for aflibercept, a recombinant fusion protein which binds circulating VEGF. In one large randomized trial of systemic use of aflibercept in metastatic colorectal cancer, epistaxis was noted in 27.7% of participants in the aflibercept group, compared to 7.4% for controls (p-value not reported) [63]. A higher risk of grade ≥ 3 bleeding was noted in the aflibercept arm, at 2.9% versus 1.7% for controls (p-value not reported).

Ibrutinib is the only currently approved Bruton's tyrosine kinase (BTK) inhibitor, used for treatment of B cell cancers including mantle cell lymphoma, chronic lymphocytic leukemia and WM. BTK participates in platelet signaling, but it is believed that additional off-target effects of the drug mediate platelet dysfunction and confer an increased risk of bleeding [64]. Mucocutaneous bleeding has been the most commonly noted event, but intracranial hemorrhage was also reported. In one randomized trial of ibrutinib for chronic lymphocytic leukemia, the risk of major hemorrhage was 4% in the ibrutinib arm and 2% in the control arm [65]. A report on the long-term follow-up of patients enrolled in a phase II mantle cell lymphoma study noted a risk of any bleeding event of 50% and a risk of grade ≥ 3 bleeding of 6% after a median follow-up of 26.7 months [66].

13.1.10 Paraneoplastic Hyperfibrinolysis

Physiological fibrinolysis of intravascular thrombi is initiated by the conversion of plasminogen to plasmin by one of several enzymes, including tissue plasminogen activator (TPA) and urokinase-type plasminogen activator (UPA). TPA is normally present in the subendothelial space, and when vascular injury occurs, clot formation is normally followed by resorption secondary to exposure of TPA. TPA is not

perfectly selective and it can also mediate fibrinogenolysis, so large amounts of this enzyme in the systemic circulation can result in decreased levels of fibrinogen.

A rare syndrome of isolated primary hyperfibrinolysis has been described in association with prostate and breast malignancies [67–70]. It is characterized primarily by mucocutaneous bleeding (easy bruising, epistaxis, menorrhagia), but has also been described in association with soft tissue hematomas. Laboratory findings include a low fibrinogen level, prolonged APTT, increased D-dimers and elevated TPA levels. The exact pathophysiological mechanism is unclear; however, expression of UPA (for prostate cancer) or TPA (for breast cancer) by the tumor might explain the observed coagulopathy [70, 71]. The successful administration of fibrinolytic inhibitors like tranexamic acid has been reported in this setting [72].

13.2 Conclusion

Cancer-associated bleeding disorders are diverse and relatively uncommon, with the notable exception of thrombocytopenic states. The coagulopathy of APL and acquired hemophilia are life-threatening emergencies which must be recognized promptly. AVWD and other less common paraneoplastic bleeding disorders tend to be more indolent in their presentation, but can result in clinically significant bleeding manifestations. In all cases, a good understanding of hemostasis and coagulation laboratory testing is necessary to make the correct diagnosis and maximize the chances of a favorable outcome.

References

1. Grimwade D, Hills RK, Moorman AV, Walker H, Chatters S, Goldstone AH, Wheatley K, Harrison CJ, Burnett AK, National Cancer Research Institute Adult Leukaemia Working Group (2010) Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. Blood 116(3):354–365. https://doi.org/10.1182/blood-2009-11-254441
2. de la Serna J, Montesinos P, Vellenga E, Rayon C, Parody R, Leon A, Esteve J, Bergua JM, Milone G, Deben G, Rivas C, Gonzalez M, Tormo M, Diaz-Mediavilla J, Gonzalez JD, Negri S, Amutio E, Brunet S, Lowenberg B, Sanz MA (2008) Causes and prognostic factors of remission induction failure in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and idarubicin. Blood 111(7):3395–3402. https://doi.org/10.1182/blood-2007-07-100669
3. Di Bona E, Avvisati G, Castaman G, Luce Vegna M, De Sanctis V, Rodeghiero F, Mandelli F (2000) Early haemorrhagic morbidity and mortality during remission induction with or without all-trans retinoic acid in acute promyelocytic leukaemia. Br J Haematol 108(4):689–695
4. Menell JS, Cesarman GM, Jacovina AT, McLaughlin MA, Lev EA, Hajjar KA (1999) Annexin II and bleeding in acute promyelocytic leukemia. N Engl J Med 340(13):994–1004. https://doi.org/10.1056/NEJM199904013401303
5. Liu Y, Wang Z, Jiang M, Dai L, Zhang W, Wu D, Ruan C (2011) The expression of annexin II and its role in the fibrinolytic activity in acute promyelocytic leukemia. Leuk Res 35 (7):879–884. https://doi.org/10.1016/j.leukres.2010.11.008

6. Cesarman GM, Guevara CA, Hajjar KA (1994) An endothelial cell receptor for plasminogen/tissue plasminogen activator (t-PA). II. Annexin II-mediated enhancement of t-PA-dependent plasminogen activation. J Biol Chem 269(33):21198–21203
7. Koyama T, Hirosawa S, Kawamata N, Tohda S, Aoki N (1994) All-trans retinoic acid upregulates thrombomodulin and downregulates tissue-factor expression in acute promyelocytic leukemia cells: distinct expression of thrombomodulin and tissue factor in human leukemic cells. Blood 84(9):3001–3009
8. Falanga A, Consonni R, Marchetti M, Locatelli G, Garattini E, Passerini CG, Gordon SG, Barbui T (1998) Cancer procoagulant and tissue factor are differently modulated by all-trans-retinoic acid in acute promyelocytic leukemia cells. Blood 92(1):143–151
9. Mantha S, Tallman MS, Soff GA (2016) What's new in the pathogenesis of the coagulopathy in acute promyelocytic leukemia? Curr Opin Hematol 23(2):121–126. https://doi.org/10.1097/MOH.0000000000000221
10. Mitrovic M, Suvajdzic N, Bogdanovic A, Kurtovic NK, Sretenovic A, Elezovic I, Tomin D (2013) International Society of Thrombosis and Hemostasis Scoring System for disseminated intravascular coagulation ≥ 6: a new predictor of hemorrhagic early death in acute promyelocytic leukemia. Med Oncol 30(1):478. https://doi.org/10.1007/s12032-013-0478-y
11. Chang H, Kuo MC, Shih LY, Dunn P, Wang PN, Wu JH, Lin TL, Hung YS, Tang TC (2012) Clinical bleeding events and laboratory coagulation profiles in acute promyelocytic leukemia. Eur J Haematol 88(4):321–328. https://doi.org/10.1111/j.1600-0609.2011.01747.x
12. Sanz MA, Grimwade D, Tallman MS, Lowenberg B, Fenaux P, Estey EH, Naoe T, Lengfelder E, Buchner T, Dohner H, Burnett AK, Lo-Coco F (2009) Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood 113(9):1875–1891. https://doi.org/10.1182/blood-2008-04-150250
13. Olwill SA, McGlynn H, Gilmore WS, Alexander HD (2005) All-trans retinoic acid-induced downregulation of annexin II expression in myeloid leukaemia cell lines is not confined to acute promyelocytic leukaemia. Br J Haematol 131(2):258–264. https://doi.org/10.1111/j.1365-2141.2005.05750.x
14. Mantha S, Goldman DA, Devlin SM, Lee JW, Zannino D, Collins M, Douer D, Iland HJ, Litzow MR, Stein EM, Appelbaum FR, Larson RA, Stone R, Powell BL, Geyer S, Laumann K, Rowe JM, Erba H, Coutre S, Othus M, Park JH, Wiernik PH, Tallman MS (2017) Determinants of fatal bleeding during induction therapy for acute promyelocytic leukemia in the ATRA era. Blood 129(13):1763–1767. https://doi.org/10.1182/blood-2016-10-747170
15. Abla O, Ribeiro RC, Testi AM, Montesinos P, Creutzig U, Sung L, Di Giuseppe G, Stephens D, Feusner JH, Powell BL, Hasle H, Kaspers GJL, Dalla-Pozza L, Lassaletta A, Tallman MS, Locatelli F, Reinhardt D, Lo-Coco F, Hitzler J, Sanz MA (2017) Predictors of thrombohemorrhagic early death in children and adolescents with t(15;17)-positive acute promyelocytic leukemia treated with ATRA and chemotherapy. Ann Hematol 96(9):1449–1456. https://doi.org/10.1007/s00277-017-3042-6
16. Levi M, Ten Cate H (1999) Disseminated intravascular coagulation. N Engl J Med 341(8):586–592. https://doi.org/10.1056/NEJM199908193410807
17. Yanada M, Matsushita T, Suzuki M, Kiyoi H, Yamamoto K, Kinoshita T, Kojima T, Saito H, Naoe T (2006) Disseminated intravascular coagulation in acute leukemia: clinical and laboratory features at presentation. Eur J Haematol 77(4):282–287. https://doi.org/10.1111/j.1600-0609.2006.00711.x
18. Dixit A, Chatterjee T, Mishra P, Kannan M, Choudhry DR, Mahapatra M, Choudhry VP, Saxena R (2007) Disseminated intravascular coagulation in acute leukemia at presentation and during induction therapy. Clin Appl Thromb Hemost 13(3):292–298. https://doi.org/10.1177/1076029607302435
19. Barbui T, Falanga A (2001) Disseminated intravascular coagulation in acute leukemia. Semin Thromb Hemost 27(6):593–604. https://doi.org/10.1055/s-2001-18865

20. Thachil J, Falanga A, Levi M, Liebman H, Di Nisio M, Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis (2015) Management of cancer-associated disseminated intravascular coagulation: guidance from the SSC of the ISTH. J Thromb Haemost 13(4):671–675. https://doi.org/10.1111/jth.12838
21. Saito H, Maruyama I, Shimazaki S, Yamamoto Y, Aikawa N, Ohno R, Hirayama A, Matsuda T, Asakura H, Nakashima M, Aoki N (2007) Efficacy and safety of recombinant human soluble thrombomodulin (ART-123) in disseminated intravascular coagulation: results of a phase III, randomized, double-blind clinical trial. J Thromb Haemost 5(1):31–41. https://doi.org/10.1111/j.1538-7836.2006.02267.x
22. Yokoyama H, Takahashi N, Katsuoka Y, Inomata M, Ito T, Meguro K, Kameoka Y, Tsumanuma R, Murai K, Noji H, Ishizawa K, Ito S, Onishi Y, Harigae H, Tohoku Hematology Forum (2017) Evaluation of the safety and efficacy of recombinant soluble thrombomodulin for patients with disseminated intravascular coagulation associated with acute leukemia: multicenter prospective study by the Tohoku Hematology Forum. Int J Hematol 105(5):606–613. https://doi.org/10.1007/s12185-017-2190-8
23. Arai M, Scandella D, Hoyer LW (1989) Molecular basis of factor VIII inhibition by human antibodies. Antibodies that bind to the factor VIII light chain prevent the interaction of factor VIII with phospholipid. J Clin Invest 83(6):1978–1984. https://doi.org/10.1172/jci114107
24. Collins PW, Hirsch S, Baglin TP, Dolan G, Hanley J, Makris M, Keeling DM, Liesner R, Brown SA, Hay CR, United Kingdom Haemophilia Centre Doctors' Organisation (2007) Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. Blood 109(5):1870–1877. https://doi.org/10.1182/blood-2006-06-029850
25. Kruse-Jarres R, Kempton CL, Baudo F, Collins PW, Knoebl P, Leissinger CA, Tiede A, Kessler CM (2017) Acquired hemophilia A: updated review of evidence and treatment guidance. Am J Hematol 92(7):695–705. https://doi.org/10.1002/ajh.24777
26. Delgado J, Jimenez-Yuste V, Hernandez-Navarro F, Villar A (2003) Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors. Br J Haematol 121 (1):21–35
27. Napolitano M, Siragusa S, Mancuso S, Kessler CM (2018) Acquired haemophilia in cancer: a systematic and critical literature review. Haemophilia 24(1):43–56. https://doi.org/10.1111/hae.13355
28. Tiede A, Priesack J, Werwitzke S, Bohlmann K, Oortwijn B, Lenting P, Eisert R, Ganser A, Budde U (2008) Diagnostic workup of patients with acquired von Willebrand syndrome: a retrospective single-centre cohort study. J Thromb Haemost 6(4):569–576. https://doi.org/10.1111/j.1538-7836.2008.02909.x
29. Federici AB, Rand JH, Bucciarelli P, Budde U, van Genderen PJ, Mohri H, Meyer D, Rodeghiero F, Sadler JE, Subcommittee on von Willebrand Factor (2000) Acquired von Willebrand syndrome: data from an international registry. Thromb Haemost 84(2):345–349
30. Mital A, Prejzner W, Bieniaszewska M, Hellmann A (2015) Prevalence of acquired von Willebrand syndrome during essential thrombocythemia: a retrospective analysis of 170 consecutive patients. Pol Arch Med Wewn 125(12):914–920
31. Mital A, Prejzner W, Hellmann A (2015) Acquired von Willebrand syndrome during the course of myelofibrosis: analysis of 32 cases. Adv Clin Exp Med 24(6):1001–1006. https://doi.org/10.17219/acem/52361
32. Mital A, Prejzner W, Swiatkowska-Stodulska R, Hellmann A (2015) Factors predisposing to acquired von Willebrand syndrome during the course of polycythemia vera—retrospective analysis of 142 consecutive cases. Thromb Res 136(4):754–757. https://doi.org/10.1016/j.thromres.2015.07.029
33. Lancellotti S, Dragani A, Ranalli P, Petrucci G, Basso M, Tartaglione R, Rocca B, De Cristofaro R (2015) Qualitative and quantitative modifications of von Willebrand factor in patients with essential thrombocythemia and controlled platelet count. J Thromb Haemost 13 (7):1226–1237. https://doi.org/10.1111/jth.12967

34. Kumar S, Pruthi RK, Nichols WL (2003) Acquired von Willebrand's syndrome: a single institution experience. Am J Hematol 72(4):243–247. https://doi.org/10.1002/ajh.10298
35. Voisin S, Hamidou M, Lefrancois A, Sigaud M, Mahe B, Trossaert M (2011) Acquired von Willebrand syndrome associated with monoclonal gammopathy: a single-center study of 36 patients. Medicine (Baltimore) 90(6):404–411. https://doi.org/10.1097/MD.0b013e3182397166
36. Dicke C, Schneppenheim S, Holstein K, Spath B, Bokemeyer C, Dittmer R, Budde U, Langer F (2016) Distinct mechanisms account for acquired von Willebrand syndrome in plasma cell dyscrasias. Ann Hematol 95(6):945–957. https://doi.org/10.1007/s00277-016-2650-x
37. Fosbury E, Szychot E, Slater O, Mathias M, Sibson K (2017) An 11-year experience of acquired von Willebrand syndrome in children diagnosed with Wilms tumour in a tertiary referral centre. Pediatr Blood Cancer 64(3). https://doi.org/10.1002/pbc.26246
38. Ali AM, Mirrakhimov AE, Abboud CN, Cashen AF (2016) Leukostasis in adult acute hyperleukocytic leukemia: a clinician's digest. Hematol Oncol 34(2):69–78. https://doi.org/10.1002/hon.2292
39. Azoulay E, Fieux F, Moreau D, Thiery G, Rousselot P, Parrot A, Le Gall JR, Dombret H, Schlemmer B (2003) Acute monocytic leukemia presenting as acute respiratory failure. Am J Respir Crit Care Med 167(10):1329–1333. https://doi.org/10.1164/rccm.200206-554OC
40. Rollig C, Ehninger G (2015) How I treat hyperleukocytosis in acute myeloid leukemia. Blood 125(21):3246–3252. https://doi.org/10.1182/blood-2014-10-551507
41. Garcia-Sanz R, Montoto S, Torrequebrada A, de Coca AG, Petit J, Sureda A, Rodriguez-Garcia JA, Masso P, Perez-Aliaga A, Monteagudo MD, Navarro I, Moreno G, Toledo C, Alonso A, Besses C, Besalduch J, Jarque I, Salama P, Rivas JA, Navarro B, Blade J, Miguel JF, Spanish Group for the Study of Waldenstrom Macroglobulinaemia and Pethema (2001) Waldenstrom macroglobulinaemia: presenting features and outcome in a series with 217 cases. Br J Haematol 115(3):575–582
42. Eby CS (2007) Bleeding and thrombosis risks in plasma cell dyscrasias. Hematol Am Soc Hematol Educ Program 158–164. https://doi.org/10.1182/asheducation-2007.1.158
43. DiMinno G, Coraggio F, Cerbone AM, Capitanio AM, Manzo C, Spina M, Scarpato P, Dattoli GM, Mattioli PL, Mancini M (1986) A myeloma paraprotein with specificity for platelet glycoprotein IIIa in a patient with a fatal bleeding disorder. J Clin Invest 77(1):157–164. https://doi.org/10.1172/JCI112270
44. Stone MJ, Bogen SA (2012) Evidence-based focused review of management of hyperviscosity syndrome. Blood 119(10):2205–2208. https://doi.org/10.1182/blood-2011-04-347690
45. Mumford AD, O'Donnell J, Gillmore JD, Manning RA, Hawkins PN, Laffan M (2000) Bleeding symptoms and coagulation abnormalities in 337 patients with AL-amyloidosis. Br J Haematol 110(2):454–460
46. Gamba G, Montani N, Anesi E, Palladini G, Capezzera M, Soldavini E, Merlini G (2000) Clotting alterations in primary systemic amyloidosis. Haematologica 85(3):289–292
47. Hoshino Y, Hatake K, Muroi K, Tsunoda S, Suzuki T, Miwa A, Sakamoto S, Miura Y (1993) Bleeding tendency caused by the deposit of amyloid substance in the perivascular region. Intern Med 32(11):879–881
48. Choufani EB, Sanchorawala V, Ernst T, Quillen K, Skinner M, Wright DG, Seldin DC (2001) Acquired factor X deficiency in patients with amyloid light-chain amyloidosis: incidence, bleeding manifestations, and response to high-dose chemotherapy. Blood 97(6):1885–1887
49. Furie B, Greene E, Furie BC (1977) Syndrome of acquired factor X deficiency and systemic amyloidosis in vivo studies of the metabolic fate of factor X. N Engl J Med 297(2):81–85. https://doi.org/10.1056/NEJM197707142970203
50. Furie B, Voo L, McAdam KP, Furie BC (1981) Mechanism of factor X deficiency in systemic amyloidosis. N Engl J Med 304(14):827–830. https://doi.org/10.1056/NEJM198104023041407

51. Litvak A, Kumar A, Wong RJ, Smith L, Hassou H, Soff G (2014) Successful perioperative use of prothrombin complex concentrate in the treatment of acquired factor X deficiency in the setting of systemic light-chain (AL) amyloidosis. Am J Hematol 89(12):1153–1154. https://doi.org/10.1002/ajh.23813
52. Thompson CA, Kyle R, Gertz M, Heit J, Pruthi R, Pardanani A (2010) Systemic AL amyloidosis with acquired factor X deficiency: a study of perioperative bleeding risk and treatment outcomes in 60 patients. Am J Hematol 85(3):171–173. https://doi.org/10.1002/ajh.21603
53. Greipp PR, Kyle RA, Bowie EJ (1979) Factor X deficiency in primary amyloidosis: resolution after splenectomy. N Engl J Med 301(19):1050–1051. https://doi.org/10.1056/NEJM197911083011907
54. Schafer AI (1984) Bleeding and thrombosis in the myeloproliferative disorders. Blood 64 (1):1–12
55. Pareti FI, Gugliotta L, Mannucci L, Guarini A, Mannucci PM (1982) Biochemical and metabolic aspects of platelet dysfunction in chronic myeloproliferative disorders. Thromb Haemost 47(2):84–89
56. Kaywin P, McDonough M, Insel PA, Shattil SJ (1978) Platelet function in essential thrombocythemia. Decreased epinephrine responsiveness associated with a deficiency of platelet alpha-adrenergic receptors. N Engl J Med 299(10):505–509. https://doi.org/10.1056/nejm197809072991002
57. Cesar JM, de Miguel D, Avello AG, Burgaleta C (2005) Platelet dysfunction in primary thrombocythemia using the platelet function analyzer, PFA-100. Am J Clin Pathol 123 (5):772–777. https://doi.org/10.1309/k58ewk4hpd51u3be
58. Elliott MA, Tefferi A (2005) Thrombosis and haemorrhage in polycythaemia vera and essential thrombocythaemia. Br J Haematol 128(3):275–290. https://doi.org/10.1111/j.1365-2141.2004.05277.x
59. Mittelman M, Zeidman A (2000) Platelet function in the myelodysplastic syndromes. Int J Hematol 71(2):95–98
60. Hapani S, Sher A, Chu D, Wu S (2010) Increased risk of serious hemorrhage with bevacizumab in cancer patients: a meta-analysis. Oncology (Williston Park) 79(1–2):27–38. https://doi.org/10.1159/000314980
61. Qi WX, Tang LN, Sun YJ, He AN, Lin F, Shen Z, Yao Y (2013) Incidence and risk of hemorrhagic events with vascular endothelial growth factor receptor tyrosine-kinase inhibitors: an up-to-date meta-analysis of 27 randomized controlled trials. Ann Oncol 24 (12):2943–2952. https://doi.org/10.1093/annonc/mdt292
62. Arnold D, Fuchs CS, Tabernero J, Ohtsu A, Zhu AX, Garon EB, Mackey JR, Paz-Ares L, Baron AD, Okusaka T, Yoshino T, Yoon HH, Das M, Ferry D, Zhang Y, Lin Y, Binder P, Sashegyi A, Chau I (2017) Meta-analysis of individual patient safety data from six randomized, placebo-controlled trials with the antiangiogenic VEGFR2-binding monoclonal antibody ramucirumab. Ann Oncol 28(12):2932–2942. https://doi.org/10.1093/annonc/mdx514
63. Van Cutsem E, Tabernero J, Lakomy R, Prenen H, Prausova J, Macarulla T, Ruff P, van Hazel GA, Moiseyenko V, Ferry D, McKendrick J, Polikoff J, Tellier A, Castan R, Allegra C (2012) Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol 30(28):3499–3506. https://doi.org/10.1200/JCO.2012.42.8201
64. Shatzel JJ, Olson SR, Tao DL, McCarty OJT, Danilov AV, DeLoughery TG (2017) Ibrutinib-associated bleeding: pathogenesis, management and risk reduction strategies. J Thromb Haemost 15(5):835–847. https://doi.org/10.1111/jth.13651
65. Burger JA, Tedeschi A, Barr PM, Robak T, Owen C, Ghia P, Bairey O, Hillmen P, Bartlett NL, Li J, Simpson D, Grosicki S, Devereux S, McCarthy H, Coutre S, Quach H, Gaidano G, Maslyak Z, Stevens DA, Janssens A, Offner F, Mayer J, O'Dwyer M,

Hellmann A, Schuh A, Siddiqi T, Polliack A, Tam CS, Suri D, Cheng M, Clow F, Styles L, James DF, Kipps TJ, RESONATE-2 Investigators (2015) Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. N Engl J Med 373(25):2425–2437. https://doi.org/10.1056/nejmoa1509388

66. Wang ML, Blum KA, Martin P, Goy A, Auer R, Kahl BS, Jurczak W, Advani RH, Romaguera JE, Williams ME, Barrientos JC, Chmielowska E, Radford J, Stilgenbauer S, Dreyling M, Jedrzejczak WW, Johnson P, Spurgeon SE, Zhang L, Baher L, Cheng M, Lee D, Beaupre DM, Rule S (2015) Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. Blood 126(6):739–745. https://doi.org/10.1182/blood-2015-03-635326
67. Kulic A, Cvetkovic Z, Libek V (2016) Primary hyperfibrinolysis as the presenting sign of prostate cancer: a case report. Vojnosanit Pregl 73(9):877–880. https://doi.org/10.2298/VSP150525076K
68. Okajima K, Kohno I, Tsuruta J, Okabe H, Takatsuki K, Binder BR (1992) Direct evidence for systemic fibrinogenolysis in a patient with metastatic prostatic cancer. Thromb Res 66 (6):717–727
69. Aulmann C, Seufert P, Sandherr M, Schlimok G, Schulze R, Oruzio D (2007) A 65-year-old female patient with breast cancer accompanied by thrombocytopenia and hyperfibrinolysis. Internist (Berl) 48(9):1015–1019. https://doi.org/10.1007/s00108-007-1920-z
70. Naina HV, Patnaik MM, Ali UA, Chen D, Ashrani AA (2010) Systemic fibrinolysis caused by tissue plasminogen activator-producing metastatic breast cancer. J Clin Oncol 28(11): e167–e168. https://doi.org/10.1200/JCO.2009.25.2502
71. Kohli M, Kaushal V, Mehta P (2003) Role of coagulation and fibrinolytic system in prostate cancer. Semin Thromb Hemost 29(3):301–308
72. Prokopchuk-Gauk O, Brose K (2015) Tranexamic acid to treat life-threatening hemorrhage in prostate cancer associated disseminated intravascular coagulation with excessive fibrinolysis. Cureus 7(12):e428. https://doi.org/10.7759/cureus.428