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