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SHORT COMMUNICATION

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Incidence of objectively diagnosed thromboembolic disease in cancer patients undergoing cytotoxic chemotherapy and/or hormonal therapy

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Abstract From August 1993 to May 1994 there were 1505 inpatient and 2590 outpatient chemotherapy treatment episodes at the Clatterbridge Centre for Oncology. A total of 21 thromboembolic events, including two arterial events, were recorded among these patients at a median of 8 weeks from the start of treatment (range 0–14 weeks), and 2 episodes occurred at the time of first presentation. The median age of the patients developing thromboembolism was 53 (range 29–75) years, and there were 14 women and 7 men. In all, 13 of the events (62%) occurred in patients receiving inpatient treatment and 8 (38%), in outpatients. The incidence of thrombosis per treatment episode in inpatients was therefore 0.008 as compared with 0.003 in outpatients. The associated malignancies were breast cancer (5), testicular cancer (4), lung cancer (3), ovarian cancer (3) and non-Hodgkin's lymphoma (2), with bladder, colon, anal and brain cancer providing 1 case each. The following bulky pelvic or para-aortic disease was present in 9 patients: testicular cancer (3), ovarian cancer (3), lymphoma (2) and bladder cancer (1). In all, 20 of the 21 thrombotic episodes were successfully treated, with 1 patient dying from the complications of venous gangrene. Thromboembolic disease is a relatively common and important cause of morbidity and mortality in cancer patients that requires early recognition and treatment.

Key words Cancer · Chemotherapy · Thromboembolism

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Introduction

The association between malignancy and the increased incidence of thromboembolism was first made by Trousseau [41] over a century ago. The link was then confirmed by Sproul [39] in a post-mortem series on patients dying of cancer. He noted a particularly high frequency of thromboembolism in patients with carcinoma of the pancreas, and similar results were subsequently reported for cancers of the lung, stomach, breast, colon, uterus and prostate [7, 15, 21, 30].

The annual incidence of deep-vein thrombosis (DVT) among hospitalised non-cancer patients is 48 per 100 000, equivalent to 0.004% per month [38]. Two factors associated with an increased risk are advancing age and a diagnosis of malignant disease. For patients in the 60- to 70-year age group the incidence per month is 0.01%, rising to 0.02% in patients aged 70–80 years. For patients with breast cancer the risk is 0.04%, a relative risk of 4, but for breast cancer patients receiving chemotherapy this risk rises to 140. The relative risk for patients with lung, pancreatic and gastrointestinal cancers are 90, 150 and 150, respectively [38]. Pulmonary embolism is the second commonest cause of death in cancer patients [9]. This paper describes the thromboembolic events seen at the Clatterbridge Centre for Oncology from August 1993 to May 1994.

Patients and methods

The Clatterbridge Centre for Oncology is a regional cancer treatment centre serving a population of 2.7 million drawn principally from Merseyside and North Wales. Inpatient chemotherapy is carried out in a modern medical oncology ward with 29 beds and an average of 35 admissions per week. In addition, outpatient chemotherapy takes place both at the centre and at affiliated district general hospitals.

The study took place during a 43-week period ranging from August 1993 to May 1994. The records of all patients receiving chemotherapy during this period were examined and all episodes of thromboembolic disease, recorded. Table 1 describes the

Table 1 Clinico-pathological features of patients with thromboembolic events (*AMI* acute myocardial infarction, *axill.* axillary, *BEP* bleomycin/etoposide/cisplatin, *BSO* bilateral salpingo-oophorectomy, *C. enzymes* cardiac enzymes, *CA* carcinoma, *CAE* cyclophosphamide/adriamycin/etoposide, *CCNU* lomustine, *Cis* cisplatin, *CMF* cyclophosphamide/methotrexate/5-fluorouracil, *CMV* cisplatin/methotrexate/vinblastine, *DVT* deep venous thrombosis, *ECG* electrocardiogram, *ED* extensive disease, *EP* etoposide/cisplatin, 5-*FU*/*L* 5-fluorouracil/levamisole, *G-CSF* granulocyte colony-stimulating factor, *Mastecto* mastectomy, *NHL* non-Hodgkin's lymphoma, *LD* limited disease, *PCD* phlegmasia cerluna Dolens, *PTE* pulmonary thromboembolism, *RT* radiotherapy, *squa* squamous, *SCLC* small-cell lung cancer, *TAH* total abdominal hysterectomy, *Tam* tamoxifen, *TE events* thromboembolic events, *TFSChe* time from the start of chemotherapy, *V. throm* venous thrombosis, *Vapec-B* 12-week combination chemotherapy, *V*/*Q scan* ventilation/perfusion scan)

No.	Sex	Age (years)	Diagnosis	Staging	Therapy	TE events	Diagnostic method	TFSChe (weeks)
01	M	32	Germ-cell tumor	IE	BEP	PCD	Venogram	14
02	F	72	Ovarian adeno-CA		S/A cisplatin	PTE	V/Q scan	6
03	M	31	Testicular seminoma	II	EP	Left leg DVT	Venogram	Presenting
04	M	46	Bladder TCC	T4N1M0	CMV	Right leg DVT	Venogram	4
05	F	58	Colonic adeno-CA	Duke C	5-FU\L	PTE	V/Q scan	8
06	F	75	SCLC	ED	CAE	Left leg DVT	Venogram	6
07	M	52	NHL	IIIB	Vapec-B	PTE	V/Q scan	9
08	M	37	Testicular seminoma	II	EP	Right leg DVT	Venogram	2
09	F	60	Anal squa. CA	T3N0M0	5-FU/RT	Right leg DVT	Venogram	4
10	F	54	Ovarian adeno-CA	III	TAH + BSO + S/A cisplatin	Left leg DVT	Venogram	3
11	F	74	Breast ductal CA	T2N0M0	Mastecto + RT + Tam	Left leg DVT	Venogram	8
12	F	69	Breast ductal CA	IV	Mastecto + RT + Tam	Left leg DVT	Venogram	9
13	F	45	Glioblastoma		Radical RT + CCNU	Left leg DVT	Venogram	4
14	F	47	Breast ductal CA	IV	CMF	AMI	ECG/C. enzymes	8
15	M	29	Testicular teratoma	IV	BOMB/ACE	Left leg DVT	Venogram	Presenting
16	F	72	Breast ductal CA	T2NOMO	Mastecto + RT + Tam	Left leg DVT	Venogram	2
17	F	30	Breast ductal CA	T1N1M0	CMF	Left femoembol	Arteriogram	10
18	M	45	SCLC	LD	CAE-GCSF	Left axill.v. throm	Venogram	3
19	M	61	SCLC	LD	CAE-GCSF	PTE	V/Q scan	2
20	F	49	Ovarian adeno-CA	IIIC	TAH + BSO + Cis & Cyclo	Right leg DVT	Venogram	4
21	F	65	NHL	III	Vapec-B	PTE	V/Q scan	6

clinicopathological characteristics of the affected patients. Treatment of deep venous thrombosis and pulmonary embolism was carried out according to standard guidelines [25].

Results

During the 43-week study period there were 1505 inpatient and 2590 outpatient treatment episodes. The cancers treated included lung, breast, colorectal, ovary, bladder, cervix and head and neck tumours as well as sarcomas and lymphomas.

A total of 21 confirmed thromboembolic events were recorded among these patients at a median of 8 weeks from the start of treatment (range 0–14 weeks), with 2 events occurring at first presentation, i.e. before the commencement of any anti-cancer therapy. The median age of the patients developing thromboembolism was 53 (range 29–75) years, and there were 14 women and 7 men. In all, 13 of the events (62%) occurred in patients receiving inpatient treatment and 8 (38%), in outpatients. The incidence of thrombosis per treatment episode in inpatients was therefore 0.008 as compared with 0.003 in outpatients. This is almost certainly an underestimate, since no policy existed for looking at this prospectively.

Among the 13 inpatients, 10 presented with deep venous thrombosis (DVT) and 3, with pulmonary embolism. Among the outpatients there were 4 episodes of DVT, 2 episodes of pulmonary embolism, 1 arterial thrombosis and 1 myocardial infarction. Of the outpatients who developed DVT, 1 was receiving chemotherapy and 3 were receiving tamoxifen alone.

The commonest associated malignancies were breast cancer (5), testicular cancer (4), lung cancer (3), ovarian cancer (3) and non-Hodgkin's lymphoma (2), with bladder, colon, anal and brain cancer providing 1 case each. Bulk pelvic or para-aortic disease was present in 9 patients as follows: testicular cancer (3), ovarian cancer (3), lymphoma (2) and bladder cancer (1).

Of the 14 episodes of DVT, 13 responded to conventional anticoagulation with heparin and warfarin. The remaining patient, a 32-year-old man with a malignant germ-cell tumour, developed venous gangrene and, despite aggressive amputation, developed multi-organ failure and died. At the time this event occurred, he was in marker remission and nearing the end of his chemotherapy.

The arterial thrombosis was treated successfully by thrombectomy and subsequent anticoagulation; patients with pulmonary embolism and myocardial infarction made uneventful recoveries.

Discussion

The increased frequency of thromboembolic disease in cancer patients may be due to a number of factors broadly related to Virchow's triad of venous stasis, vessel-wall damage and altered blood constituents. However, the state of hypercoagulability associated with malignancy remains difficult to define. Furthermore, the diversity in underlying cellular pathology, treatment strategies (e.g. surgery, prostheses, chemotherapy) may also contribute to the risk of thrombotic events. Thromboembolic disease in cancer patients is associated with a significant increase in mortality and morbidity, with pulmonary embolism rating as the second commonest cause of death [9].

Venous stasis may be exacerbated by inactivity due to the anergy common in cancer patients and by loss of muscle bulk, which helps to maintain normal venous flow. Immobility is often more pronounced in hospitalised patients, which may partly explain the increased frequency of thromboembolic events observed in this group in our series. In addition to generalised inactivity predisposing to venous stasis, local pressure by tumour masses is a potent cause of problems. Pelvic disease compressing the ileo-femoral veins and para-aortic lymphadenopathy resulting in pressure on the inferior vena cava may result in major venous obstruction. This mechanism contributed to the development of the thrombosis in 9 of the patients described in this series, 3 of whom had bulk para-aortic disease due to metastatic testicular cancer. A high frequency of vascular events in similar patients has previously been reported by Cantwell et al. [4, 5], who suggested that the increased risk was associated with disease measuring >5 cm in diameter. Vessel-wall damage may occur in cancer patients due to direct tumour invasion, the presence of venous catheters or the vesicant effect of chemotherapeutic agents, which is most noticeable in the veins into which the drugs are infused, but distant effects also occur. In addition to the vesicant effects, a chronic Raynaud's-type phenomenon may occur principally in association with bleomycin treatment. This usually develops some months following the completion of chemotherapy [16, 42].

The normal coagulation homeostasis has been shown to be disturbed in cancer patients; levels of clotting factors, including factors V, VII, VIII, IX and XI and fibrinogen, may be increased and levels of coagulation inhibitors, low [18, 27, 34, 36]. Direct activation of the coagulation cascade by tumour cells may occur, involving both the intrinsic and the extrinsic pathways, especially if vascular invasion is present. Two procoagulants, tissue factor and cancer procoagulant, are emerging as significant, although the list of the potential procoagulants in such patients is extensive [12]. Tissue factor (TF) is a single-chain transmembrane glycoprotein that is the normal cellular initiator of coagulation; its extracellular domain acts as a receptor for factor VII and activated factor VII (VIIa), and the TF-VIIa complex is the physiological activator of factors IX and X. TF is found in many normal cells, in particular in the vascular wall and the brain; it is also present in many tumour cells and can be found in the blood as a result of shedding of the membrane vesicles [2, 6, 10–12, 27]. Kakkar et al. [27] found an increase in TF levels of 67% in the median with a concomitant rise in F(VIIa) of 40%, indicating extrinsic pathway activation; the intrinsic cascade was also activated as manifested by a 50% increment of F(XIIa) levels [27].

Cancer procoagulant (CP) is a cysteine proteinase that can activate factor X directly, bypassing the factor VII pathway, as these effects are demonstrable in factor VII-deficient plasma; it is present in extracts from a wide variety of neoplasms and its levels are elevated in the serum of the majority of cancer patients, but it is not present in normal tissues. CP appears to activate factor X by cleavage at a point in the heavy chain different from that cleaved by serine proteases [19].

Other abnormalities in cancer patients include thrombocytosis and reduced fibrinolytic activity [1]. Chemotherapy can induce protein C and S deficiencies [16], both of which are naturally occurring anticoagulants. Levels of antithrombin III, a third natural anticoagulant, have been shown to be reduced in patients receiving adjuvant chemo/hormonal therapy for breast cancer [13, 20, 26, 28, 31, 37]. Other chemotherapeutic agents such as L-asparaginase are well known to reduce antithrombin III to low levels, requiring antithrombin III concentrate replacements in conjuction with anticoagulant therapy. This agent can also lead to depletion of vitamin-K-dependent clotting factors, including factors II, VII, IX and X, and of proteins S and C [24].

Tamoxifen, a non-steroid anti-estrogen with significant benefit in the treatment of breast cancer, has been shown to cause venous thromboembolic diseases and, rarely, arterial thrombosis [9]. Antithrombin III functional activity was found to be reduced in 42% of those patients receiving tamoxifen by Enck and Rios [13]. Similar reductions in antithrombin III levels were found by other investigators in a randomised placebo-controlled trial of tamoxifen given at 10 mg twice daily for patients with breast carcinoma after 6 months of treatment [32]. Raised levels of cardiolipin antibodies have been reported in some patients with epithelial malignancies. In one study of women with stage II breast cancer [28] the overall incidence of thrombotic events in patients receiving chemotherapy was 6.8%, rising to 10.3% in patients aged over 50 years. No thromboembolic event was recorded in patients not receiving chemotherapy. In two additional studies of breast cancer patients receiving mainly cyclophosphamide/methotrexate/5-fluorouracil (CMF) chemotherapy [17, 43], the incidence of thrombotic events ranged from 5% to 18%. As mentioned above,

tamoxifen is also associated with coagulation abnormalities, and three of the patients in our series were receiving tamoxifen alone. As might be anticipated, the combination of tamoxifen and chemotherapy appears to have an additive effect on the risk for thrombosis [22, 23, 26, 31, 35].

Another factor predisposing patients to a thrombotic tendency is the widespread use of central venous catheters (CVC). CVC-related thrombosis may be attributed to several factors, including the use of rigid or thrombogenic material, sepsis, difficulty in catheter insertion, hypercoagulability and certain properties of the infusate such as low pH or high osmolarity [33, 44], as is the case with chemotherapy agents and total parenteral nutrition. Similar problems are encountered in patients undergoing regional chemotherapy as in hepatic-artery infusion for liver metastasis. None of the patients included in this survey had a CVC.

Although CP is tumour-specific, whether there is any correlation between it and the risk for clinical thromboembolic complications has yet to be found. Some of the biochemical markers of hypercoagulability that are currently being evaluated to help identify those cancer patients at increased risk for thrombotic events include D-dimers, prothrombin fragments F1 + 2 (PF1 + 2), fibrinopeptide A, and thrombin-anti-thrombin (TAT) complexes [3, 14, 40]. Kakkar et al. [27] found a 3- to 4-fold increase in TAT/PF1 + 2, indicating an excess of thrombin generation. In a preliminary study on 117 cancer patients undergoing surgery, Falanga et al. [14] found that high levels of TAT identified patients at higher risk of developing postoperative DVT.

In an effort to reduce the risk for thrombosis in cancer patients, anticoagulant prophylaxis has been investigated. Levine et al. [29] randomly allocated patients receiving chemotherapy for metastatic breast cancer to warfarin given at 1 mg daily or placebo continuing for 1 week after the completion of treatment. There were seven events (0.04%) in the placebo group and one in the warfarin group, a relative risk reduction of about 85%. Prophylactic anticoagulation with low-dose warfarin is thus effective and not associated with increased bleeding problems. However, the incidence of thromboembolism in the placebo group in this study was relatively low, and prophylaxis had no effect on survival.

In conclusion, malignant disorders with their pathological and therapeutic diversity represent a definite thrombophilic state that is difficult to characterise but contributes significantly to mortality and morbidity in these patients. Pulmonary embolism is the second commonest cause of death. A high index of suspicion has to be maintained by the clinician caring for such groups, along with a low threshold for initiating specific measures to prevent and/or treat so as to avoid a potentially lethal complication.

Some of the markers for hypercoagulability may prove to be useful in the selection of patients at particularly high risk for thromboembolic events but will be available only to a minority of clinicians; therefore, selection must continue to be based on individual merits and be done according to the physician's discretion. Immobility, pelvic masses compressing pelvic veins, and dual-modality therapy are predisposing factors; adequate hydration and encouragement of early mobility may help to prevent some of these complications.

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