Incidence of Venous Thromboembolism during Chemotherapy for Breast Cancer: Impact on Cancer Outcome

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Abstract. *Background: Evidence suggests that cancer patients who develop venous thromboembolism (VTE) have a poorer outcome than those who do not. The aim of this prospective study was to assess the incidence of the development of VTE in breast cancer patients commencing chemotherapy and the relationship between development of thrombosis and cancer progression and death. Patients and Methods: One hundred and thirty-four breast cancer patients were recruited and followed up prior to chemotherapy and at 3, 6, 12 and 24 months. Duplex ultrasound imaging (DUI) was performed 1 month following commencement of chemotherapy or if patients became symptomatic. Results: Thirteen patients developed VTE. Six patients with advanced breast cancer and seven with early breast cancer developed VTE. Three patients died from VTE; all had advanced breast cancer. In patients with VTE, the 28-day mortality rate was 15%, but in patients with symptomatic VTE, the 28-day mortality was 22%. Development of VTE did not predict for progression by three and six months in advanced breast cancer patients. VTE demonstrated a trend for predicting progression by two years. Using Cox regression survival analysis, there was no survival advantage in those with or without VTE. Conclusion: Although the body of evidence supports a worse prognosis when VTE and cancer coexist as compared to either diagnosis alone, a larger prospective study is required to confirm this and clarify whether any premature death is primarily due to VTE or to more aggressive cancer.*

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Published data on the frequency of venous thromboembolism (VTE) during chemotherapy is limited; the majority of published studies focus on chemotherapy during breast cancer. In the absence of chemotherapy, the risk of VTE in early breast cancer is between 0.2% and 0.8% (1-3), rising to 2 to 10% if the patient receives chemotherapy (4-7). The rate of VTE in advanced cancer increases further (8). In patients with advanced breast cancer receiving chemotherapy, as many as 17.6% develop VTE (9). Most reported VTEs occur early in treatment (within the first 3 cycles) (5, 6, 9-11). The rate of VTE during neoadjuvant chemotherapy has not previously been studied.

There is some evidence that cancer patients who develop VTE have a poorer cancer outcome than those who do not (12-15), suggesting that VTE may be a surrogate marker for more aggressive disease.

The aim of this prospective study was to assess the incidence of the development of VTE in breast cancer patients commencing chemotherapy. The relationship between the development of thrombosis and cancer progression and death was also investigated.

Patients and Methods

Patients. Eighty-seven patients with early breast cancer (EBC) after complete surgical resection and commencing adjuvant treatment, 11 with breast cancer (NBC) with large or inflammatory tumours commencing neoadjuvant chemotherapy and 36 with advanced breast cancer (ABC) commencing palliative treatment for radiographically proven metastatic disease were recruited.

Protocol. A prospective cohort study was undertaken. Patients were recruited prior to commencing chemotherapy. Clinical and radiological follow-up was at three, six, twelve and twenty-four months. Cancer outcome at each time point was categorised as 'response', 'stable', 'progression' or 'death', with response defined as ≥50% decrease in measureable disease (clinical or radiological) and progression defined as ≥25% increase in measureable disease (clinical or radiological). Duplex ultrasound imaging (DUI) was

Table I. *Age of patients recruited. Results are expressed as mean (range) years.*

Group (n)	Age, years (range)
Advanced breast cancer (36)	55.8 (34-78)
Early breast cancer (87)	51.3 (31-74)
Neoadjuvant breast cancer (11)	46.1 (35-58)

Table II. *Receptor positivity (+) and negativity (–) for each patient group.*

	ABC +/–	EBC +/–	NBC +/–	Total +/–	Significance of difference between groups (*p*-value)
Oestrogen	20/16	60/27	5/6	85/49	0.16
Progesterone	16/19	47/40	4/7	67/66	0.45
Her2	10/18	16/32	4/5	30/55	0.82

ABC, Advanced breast cancer; EBC, early breast cancer; NBC, neoadjuvant breast cancer.

performed one month following the commencement of chemotherapy or if patients became symptomatic.

Inclusion criteria. Women aged over 18 with i) ABC: confirmed metastatic breast cancer prior to commencement of chemotherapy (CMF (cyclophosphamide, methotrexate and 5-fluorouracil); FEC (5-fluorouracil, etoposide and cyclophosphamide) or a taxane and/or epirubicin); ii) EBC: newly diagnosed breast carcinoma who have undergone apparently curative surgery and have no clinical or radiological evidence of residual disease but who will undergo adjuvant chemotherapy (CMF and FEC); or iii) NBC: newly diagnosed breast carcinoma, with no clinical or radiological evidence of advanced disease receiving neoadjuvant chemotherapy prior to curative surgery (AC (cyclophosphamide and adriamycin) or epirubicin and navelbine), because of large primary tumour size or significant markers of tumour aggression.

Exclusion criteria. Recent surgery (<18 days), or chemotherapy (<2 months), impaired liver or renal function (>50% above upper limit of normal), thrombophilia, anticoagulant therapy (excluding aspirin, clopidogrel), hormone therapy, past history of VTE, WHO performance status ≥3 (16).

Ethical approval. The study was approved by the South Manchester Local Research Ethics Committee and all patients gave written informed consent.

Statistical methods. One-way ANOVA and independent *t*-tests were used to compare independent samples. Binary logistic regression was used to identify predictors of VTE or disease progression. Cox regression survival analysis was used to assess survival.

Results

Patient demographics. One hundred and thirty-four breast cancer patients were recruited. Of these 36 were ABC, 87 were EBC following curative surgery and 11 were NBC patients undergoing chemotherapy prior to curative surgery. There was a trend for the advanced group to be older than the neoadjuvant group, although this did not reach statistical significance (p=0.09; Table I).

There was no difference in frequency of oestrogen, progesterone or HER2 receptor positivity between patient groups. More women with ABC were postmenopausal compared to EBC and NBC (Tables II and III).

Prevalence of VTE in ABC versus EBC patients undergoing chemotherapy. Overall, thirteen (10%) patients developed VTE, of whom 9 (7%) were symptomatic. Six out of 36 (17%) ABC patients and seven out of 87 (8%) EBC patients developed VTE. None of the 11 NBC patients developed VTE. The higher rate of VTE in ABC compared to EBC approached significance (p=0.06). Of the patients with symptomatic VTE, 4 out of 36 (11%) were in the ABC group and 5 out of 87 (6%) were in the EBC group

Three (2.2%) out of 13 patients died from VTE; all had advanced breast cancer (8.3%). All three developed VTE within the first three months of commencement of chemotherapy. Survival from entry into the study for these three patients was 55, 66 and 879 days. The former two patients died within 1 and 7 days, respectively, of the development of VTE. The latter patient was found to have a calf vein thrombosis at screening, but died over two years later of pulmonary embolism. Of patients with VTE (symptomatic and screen detected), the 28-day mortality rate was 15%, but of patients with symptomatic VTE, the 28-day mortality was 22%.

Nine out of the 13 (69%) patients that developed VTE did so within the first 3 months of commencing chemotherapy. All six ABC patients who developed VTE did so within 3 months, but only three out of the seven EBC patients developed VTE within 3 months of starting adjuvant chemotherapy.

Ten out of the 13 (77%) VTE events occurred in postmeno-pausal women, however neither age, nor menopausal status was associated with an increased risk of VTE (p=0.2 and 0.2 respectively). Development of VTE in the EBC group did not correlate with the number of days from surgery to commencing chemotherapy (p=0.7).

Cancer outcome. Cancer outcome was categorised into 'response', 'stable', 'progression' and 'death' at 3, 6, 12 and 24 months (Table IV).

Development of VTE did not predict for progression by 3 and 6 months in ABC patients (p=0.17 and 0.15 respectively). VTE demonstrated a trend for predicting progression by two years (p=0.08 for EBC patients and

Table III. *Numbers of pre- and postmenopausal women in each patient group. The ratio of pre- to postmenopausal women in advanced breast cancer is compared to the ratio of pre- to post menopausal women in other groups (Chi-squared).*

	Premenopausal	Postmenopausal	Significance (*p*-value)
Advanced breast cancer (36)	9	27	
Early breast cancer (87)	39	48	0.05
Neoadjuvant breast cancer (11)	8	3	0.009

p=0.07 for all cancer patients on logistic regression). Using Cox regression survival analysis there was no survival advantage for those with or without VTE (p=0.4).

Discussion

Prevalence of VTE in advanced versus early breast cancer patients undergoing chemotherapy. The rate of VTE during chemotherapy in both the EBC and ABC groups in this study concurs with much of the current literature (4-7, 9). Despite difficulties with recruitment within the limitations of study time, we were able to confirm the previously quoted literature on the rate of VTE, and the increased rate that occurs in ABC compared to EBC. In accordance with much of the previous literature, 69% (9 out of 13) of the VTEs in this current study occurred within three months of commencing chemotherapy (5, 6, 9-11). However, in a recent study of 381 breast and gastrointestinal patients commencing chemotherapy, the mean time to VTE (occurring in 30 patients) was four months (7). Although many studies with VTE as an endpoint use venography to screen for deep vein thrombosis, we used DUI. The quality of imaging in our unit is extremely high, with a high rate for identifying even asymptomatic VTE. This non-invasive test allowed increased patient compliance and is well recognised as a screening tool for VTE (17-19).

Saphner *et al*. reported a 0.8% (4 out of 471) VTE rate in premenopausal women receiving adjuvant chemotherapy (3). Weiss *et al*. prospectively reported a 5% (22 out of 433) VTE rate in node-positive breast cancer patients receiving adjuvant chemotherapy (6). Both studies relied on clinical presentation (either as an emergency by the patient or by examination at follow-up by the physician), rather than screen detection. A 9% (9 out of 102) and 10% (5 out of 50) VTE rate in node-positive, EBC patients receiving chemotherapy, as detected by impedence plethysmography and DUI screening, was found by Levine *et al*. (4) and von Templehoff *et al*. (5) respectively. The more recent study of Mandala *et al*. reported a 8.8% (16 out of 182) rate of symptomatic VTE in consecutive breast cancer patients commencing adjuvant chemotherapy (7). This increased rate of symptomatic VTE compared to older studies may reflect an increased awareness of the symptoms of deep vein thrombosis amongst patients as a result of media focus on flight-related thrombosis. Levine *et al*.'s 1994 study of ABC patients receiving chemotherapy and randomised to warfarin or no treatment reported a VTE rate of only 4.4% (20). In their study however, VTE screening was by clinical methods only. Patients recruited to the study had already commenced chemotherapy, and so those patients developing VTE early in response to chemotherapy would have been excluded. As this appears to be the majority of patients (5, 6, 9-11) this biases the recruited population to a low risk group. A more recent study of vinorelbine, cisplatin and 5-fluorouracil in ABC patients reports an 8% (8 out of 100) symptomatic VTE rate (21). This present study is not empowered to confirm the

Table IV. *Response to treatment. Results show the number of patients that had radiological or clinical cancer progression or response within three to twenty-four months. The cumulative number of patient deaths (either from VTE or cancer) is reported in the fifth column. The cumulative number of patients developing VTE in each group is reported in brackets, with total numbers reported in the last column.*

	Response	Stable	Progression	Death (cumulative)	VTE (cumulative)
3 Months					
ABC	15 (2)	6	9 (2)	6 (2)	6
EBC	0	87 (3)	0	0	3
NBC	9	2	0	0	
Total	24 (2)	95 (3)	9 (2)	6 (2)	9
6 Months					
ABC	4	10	11 (3)	11 (3)	6
EBC	0	87 (5)	0	0	5
NBC	0	11	0	0	
Total	4	108 (5)	11 (3)	11 (3)	11
12 Months					
ABC	1	3	10 (3)	22 (3)	6
EBC	0	85 (6)	1	1	6
NBC	0	10	0	1	
Total	1	98 (6)	11 (3)	24 (3)	12
24 Months					
ABC	1	3	2 (2)	30 (4)	6
EBC	0	81 (5)	5 (2)	1	7
NBC	0	7	2	2	
Total	1	91 (5)	9 (4)	33 (4)	13

ABC, Advanced breast cancer; EBC, early breast cancer; NBC, neoadjuvant breast cancer.

previously quoted VTE mortality in EBC of 0.2-0.5% (6, 22), however, with a mortality rate of 8%, it does confirm Goodnough *et al*.'s finding of a 7% VTE mortality rate during chemotherapy for advanced breast cancer (9).

The 28-day mortality rate for symptomatic VTE of 22% is similar to that reported by Cushman *et al*.'s cohort study, where a 28-day fatality rate after first time VTE of 11% was found, but this increased to 25% for cancer-associated thrombosis (23). Due to limited availability of eligible patients, and hence low recruitment, this study has insufficient numbers to assess the risk of VTE in patients receiving neoadjuvant chemotherapy.

Some authors reported an increased risk of thrombosis amongst postmenopausal women (3, 6, 22), however, an association was not demonstrated in this study. Saphner *et al*. (3) demonstrated oestrogen receptor positivity as a risk factor for chemotherapy induced VTE however this is not supported by Levine *et al*. (4), Clahsen *et al*. (22) or indeed the present study. This implies that Saphner *et al*.'s findings may have been due to chance.

In malignancy, haemostatic markers of coagulation are raised for several weeks after surgery (24, 25). A multicentre, double-blind, randomised, placebo-controlled study of cancer patients undergoing abdominal surgery compared prolonged (four-week) VTE prophylaxis with the standard one-week regimen. There was a 60% reduction in the relative risk of VTE in patients receiving prolonged prophylaxis (4.8% *versus* 12%, p=0.02) (26). These results have been supported by further meta-analysis (27). Reducing the interval between surgery and adjuvant chemotherapy by administering chemotherapy within 36 hours of mastectomy has been shown to prolong disease-free survival in node-negative breast cancer patients (28), however the impact on hypercoagulability of a further treatment in already recovering and inactive patients has yet to be established. In this study, there is no demonstrable added risk for VTE by commencing chemotherapy shortly after surgery. One potential weakness of this current study is that screening for VTE was not performed prior to commencement of chemotherapy. Identified thrombi could have been pre-existing and therefore be the result of the cancer, or in the case of the EBC patients, a result of surgery. This, however, increases the significance of the greater VTE rate in patients with high tumour load (advanced breast cancer).

It is recognised that these two study groups, EBC and ABC, are heterogeneous for chemotherapy type. It is also recognised that the ABC patients are heterogeneous for their site of metastatic disease.

Does development of VTE predict for a worse cancer outcome? Previous research has shown that patients who develop VTE have a worse cancer outcome than those that remain free of VTE complications (13, 14, 29-31). However, to date, all studies have been retrospective. Both Seward *et al*. and Morgan *et al*. studied medical records of cancer patients presenting with VTE at major medical centres. Seward *et al*. found that cancer patients who developed VTE had a worse prognosis than those who remained free of VTE, but failed to account for more minor VTE that may have presented to smaller district hospitals, and thus not included in the data collection (31). Morgan reported a significantly reduced survival time if cancer presented concurrently with VTE compared to a matched control group without VTE (p<0.001) (13). Chew *et al*. highlight the increased rate of VTE within the first year of cancer diagnosis, however this may reflect intensity of treatments following a new diagnosis, with many cancer treatments including surgery, radiotherapy, hormone therapy as well as chemotherapy recognised as risk-factors for VTE (32, 33). Sorensen *et al*.'s retrospective study of the National Registry acknowledges that VTE occurs more commonly in patients with more advanced disease compared to those with early cancer. This may contribute to the reduced survival in patients with VTE in cancer, seen in this study, and hence biased survival analysis (29). Levitan *et al*.'s study of Medicar records, although finding a significantly reduced survival in patients presenting with concurrent VTE, compared to cancer alone, has a similar limitation (30). However, Chew *et al*.'s retrospective review of breast cancer patients hospitalised with VTE between 1993 and 1995 reports VTE as a significant risk factor for death, even when cancer is stratified for stage (15). The increased VTE rate in advanced cancer is supported in the present study. Interestingly in Weiss *et al*.'s observational study of EBC patients commencing adjuvant chemotherapy, 35% (7 out of 20) of those with VTE developed recurrence of their breast cancer within two years, compared to 15% for the entire group of patients in the study (65 out of 433). Statistical significance was not reported (6). A recent study of cancer patients incidentally diagnosed with pulmonary embolism, on staging computed tomography, compared to symptomatic patients (matched for cancer type and stage) reported no difference in mortality (34).

The current study suggests that development of VTE may predict for cancer progression. VTE within 3 months following chemotherapy suggests a poorer outcome (p=0.07). However, with cancer progression occurring in 61% of the ABC group and none of the EBC group at 3 months, and 89% and only 7% respectively by 2 years, any analysis is complicated by strong covariates.

Although the body of evidence supports a worse prognosis when VTE and cancer coexist as compared to that with either diagnosis alone, a larger prospective study is required to confirm this and clarify whether any premature death is primarily due to VTE or to more aggressive cancer.

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