ORIGINAL ARTICLE

Risk of venous thromboembolism in patients receiving adjuvant chemotherapy with 5-fluorouracil, epirubicin and cyclophosphamide for early breast cancer

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Abstract

Aim: Previous studies have shown that adjuvant chemotherapy in early breast cancer (EBC) may increase the risk of venous thromboembolism (VTE). Clinical experience suggests the combination of 5-fluorouracil, epirubicin and cyclophosphamide (FEC) may be associated with a higher frequency of VTE than other regimens. This study aims to investigate the use of adjuvant FEC compared with other adjuvant regimens in the development of VTE in patients with EBC.

Methods: A retrospective audit was conducted examining all eligible patients who received adjuvant chemotherapy for EBC in the Australian Capital Territory from 1 January 2005 to 30 June 2007. Data were collected from patients' notes, including risk factors for VTE, tumor pathology, chemotherapy details and incidence of VTE. Comparisons using χ^2 tests and independent samples *t*-tests were made between patients who received FEC and those who received another regimen. Multivariate logistic regression was used to investigate prognostic factors for the development of VTE.

Results: A total of 325 patients were included in the study, of whom 176 received FEC and 149 received other adjuvant chemotherapy regimens. The incidence of VTE in patients who received FEC was 47/176 (27%), which was significantly higher than for patients who received other regimens (7/149, 5%, $P < 0.001$). FEC was the only significant prognostic factor for the development of VTE (OR 7.9, 95% CI 3.3–19.2, $P < 0.001$).

Conclusion: The use of adjuvant FEC chemotherapy is associated with an increased incidence of VTE in patients with EBC compared with other commonly used chemotherapy regimens.

Key words: adjuvant chemotherapy, early breast cancer, FEC, venous thromboembolism.

INTRODUCTION

There is a strong association between malignancy and the development of venous thromboembolism (VTE) although the exact mechanism for the association remains unknown.^{1–3} It is believed that tumor cells enhance pro-coagulant pathways such as the coagulation cascade and also inhibit anticoagulant properties.⁴

The development of VTE is a leading cause of death among cancer patients and is also associated with significant morbidity, including local symptoms such as pain and swelling, the risk of pulmonary embolization, the need for long-term anticoagulation and the accompanying risk of bleeding.^{3,5,6}

Although breast cancer is associated with a lower incidence of VTE compared with other common malignancies its consequences for morbidity and mortality remain significant.⁷ In patients with breast cancer the presence of metastatic disease is the most significant risk factor for the development of VTE, although the effect of VTE on survival is greater for patients with early stage disease.⁸

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Studies in patients with early breast cancer (EBC) have demonstrated an additional increase in the risk of VTE associated with the use of chemotherapy and hormonal therapy.^{9–13} Proposed mechanisms for chemotherapy-related thrombosis include the release of pro-coagulants from tumor cells, endothelial damage and stimulation of tissue factor activity in monocytes and macrophages.^{4,14,15}

Despite being a known risk factor for the development of VTE in breast cancer patients little is known about which chemotherapy regimens are associated with the greatest risk. A number of studies have looked at the incidence of thrombosis associated with cyclophosphamide, methotrexate and 5-fluorouracil (CMF), a commonly used regimen for EBC before the introduction of anthracycline-based chemotherapy.^{10,11,13} However, limited studies have investigated the risk of thrombosis with newer regimens.^{9,12} We suspected an increased incidence of VTE in women having 5-fluorouracil, epirubicin and cyclophosphamide (FEC) compared with other adjuvant chemotherapy regimens used in our clinical practice.

In the current study we aimed to identify the incidence of VTE in a cohort of patients with EBC and specifically investigate the incidence of VTE associated with adjuvant FEC compared with other adjuvant regimens. Additionally, we aimed to examine the possibility of patient variables that may be used as prognostic factors for the development of VTE.

METHODS

Data were collected from all patients who received adjuvant chemotherapy for the treatment of EBC in the Australian Capital Territory (ACT) from 1 January 2005 to 30 June 2007. The study was exempt from ethics approval by the ACT human research ethics committee as it met the guidelines for a clinical audit. Data were obtained from four sites including the Canberra Hospital, the National Capital Private Hospital, Zita Mary Clinic at Calvary Hospital and John James Private Hospital.

Patients who received any treatment with i.v. cyclophosphamide over the specified time period were identified using information obtained from the pharmacy department at each site. As all adjuvant breast cancer regimens used in the ACT during this period included i.v. cyclophosphamide, this captured the group of interest. Patients without breast cancer or with metastatic disease were then excluded by reviewing their records or by checking with the treating physician. The inclusion criteria

included a diagnosis of EBC, no evidence of metastatic disease at diagnosis and treatment with adjuvant chemotherapy where the first cycle of treatment was commenced between 1 January 2005 and 30 June 2007.

Each record was reviewed and data from those patients who met the inclusion criteria were collected including the patients' characteristics, tumor pathology, chemotherapy regimen and incidence of VTE (superficial or deep), as well as the method of detection where applicable. Patients' data collected at the first cycle of chemotherapy included their age, height, weight, body surface area, concomitant medications, smoking status, menopausal status and previous history of thrombosis. In cases where menopausal status was not indicated in the clinical history, women under the age of 50 years were considered premenopausal and those aged 50 years and above were considered postmenopausal. Their body mass index (BMI) was calculated using a standard equation and used as a comparative measure of weight, scaled to height. The normal range for healthy weight is between 20 and 25 kg/m².¹⁶

Their recorded tumor pathology included the histological type of breast cancer (ductal, lobular or other), the tumor grade, stage (International Union against Cancer, UICC),¹⁷ hormone receptor status and human epidermal growth factor 2 (Her 2/Erb B2) status. Tumors that were either or both estrogen or progesterone receptor positive were recorded as hormone receptor positive.

The information regarding chemotherapy included the type of regimen, number of cycles received and the route of i.v. administration (by peripheral cannula or by a central venous catheter). For those patients with an identified VTE, the following data were also recorded: the type of VTE, its location, the method of detection and the cycle of chemotherapy. Incidents of thrombosis were classified as superficial, including superficial thrombophlebitis and superficial or deep venous thrombosis, including central line associated thrombosis, deep venous thrombosis (DVT) and pulmonary embolus (PE). Veins in the arm were considered deep if they corresponded to an artery of the same name.

Statistical analysis

All data were analyzed using SPSS software version 16 (SPSS, Chicago IL, USA). The patients were split into two groups: those who received treatment with FEC, either alone or as part of a sequential regimen of adjuvant chemotherapy such as FEC followed by a taxane, and those who did not receive any FEC. Baseline characteristics were summarized by group, using means

and standard deviations (SD) for continuous data, and frequency and percentage for categorical data. Differences in baseline characteristics between the two groups were assessed using an independent samples *t*-test for continuous data and a χ^2 test for categorical data. An exact χ^2 test using a Monte Carlo simulation was used in cases where expected cell counts were less than five. Logistic regression was used to assess the effect of possible prognostic factors for the development of VTE and to assess the association between FEC and the risk of VTE, when adjusting for any identified factors. All significance tests were two-sided and *P*-values less than 0.05 were considered statistically significant.

RESULTS

In total, 492 patients received treatment with intravenous cyclophosphamide over the specified time period, of which 323 were eligible for inclusion in the study. Three additional patients were included who did not satisfy the initial criteria because the primary tumor was

not identified. However, each received adjuvant chemotherapy in concordance with the treatment for EBC as they presented with axillary lymphadenopathy and were assumed to have an occult breast cancer and were therefore deemed suitable. Data were insufficient for one patient, resulting in her removal from the study. Therefore, the final study population consisted of 325 patients from all four sites.

Patient characteristics

The patient characteristics are detailed in Tables 1 and 2. Most of the patients were postmenopausal (60%), although their mean age at the first cycle of chemotherapy was 51.4 years ($\pm$ SD 10.2). Their mean BMI was slightly above the normal range at 27 kg/m² ($\pm$ SD 5.5). Only 18 patients (5.5%) had a documented history of previous venous thrombosis ranging from superficial thrombophlebitis to DVT and PE.

The patients' characteristics were well matched between the two groups with no statistically significant differences in continuous or categorical variables except

Table 1 Continuous patient characteristics for the entire cohort (total *n* = 325) and for each patient group (5-fluorouracil, epirubicin and cyclophosphamide [FEC] *n* = 176, non-FEC *n* = 149)

	Total				FEC		Non-FEC		<i>P</i>
	Min	Max	Mean	SD	Mean	SD	Mean	SD	
Age (years)	28	76	51.4	10.2	52.6	10.0	50	10.4	0.02*
Weight (kg)	43.4	142	71.7	15.1	72.7	15.6	70	14.5	0.16
Height (cm)	145	181	162.5	6.3	162	6.4	162.5	6.3	0.88
BMI (kg/m ²)	17	50	27	5.5	27.6	5.6	26	5.4	0.14

*Statistically significant difference at the *P* < 0.05 level (independent samples 2-tailed *t*-test). BMI, body mass index; SD, standard deviation.

Table 2 Categorical patient characteristics for the entire cohort (total *n* = 325) and for each patient group (5-fluorouracil, epirubicin and cyclophosphamide [FEC] *n* = 176, Non-FEC *n* = 149)

		Total		FEC		Non-FEC		<i>P</i>
		<i>n</i>	% total	<i>n</i>	% total	<i>n</i>	% total	
Menopause	Pre	131	40.3	67	38	64	43	0.37
	Post	194	59.7	109	62	85	57	
Smoker	Yes	46	14.2	23	13	23	15	0.33
	No	235	72.3	133	76	102	68	
	Unknown	44	13.2	20	11	24	17	
Past history thrombosis	Yes	18	5.5	9	5.1	9	6.0	0.97
	No	299	92	163	92.6	136	91.3	
	Unknown	8	2.5	4	2.3	4	2.7	
Venous access	Peripheral	223	68.6	116	66	107	71.8	0.25
	Central	102	31.4	60	34	42	27.2	

Table 3 Tumor characteristics for the entire cohort (total $n = 325$) and for each patient group (5-fluorouracil, epirubicin and cyclophosphamide [FEC] $n = 176$, Non-FEC $n = 149$)

		Total		FEC		Non-FEC		<i>P</i>
		<i>n</i>	% total	<i>n</i>	% total	<i>n</i>	% total	
Type	Ductal	283	87.1	148	84.1	135	90.6	0.18
	Lobular	29	8.9	20	11.4	9	6.0	
	Other	13	4.0	8	4.5	5	3.4	
Grade	1	23	7.1	12	6.8	11	7.4	0.43
	2	108	33.2	56	31.8	52	34.9	
	3	192	59.1	108	61.4	84	56.4	
	Unknown	2	0.6	0	0	2	1.3	
Stage [†]	I	55	16.9	23	13.1	32	21.5	0.10
	II	183	56.3	101	57.4	82	55.0	
	III	87	26.8	4	29.5	35	23.5	
Hormone receptor	Positive	238	73.2	143	81.2	95	63.8	<0.001*
	Negative	87	26.8	33	18.8	54	36.2	
Her 2 Expression	Positive	67	20.6	33	18.8	34	22.8	0.68
	Negative	252	77.5	140	79.5	112	75.2	
	Unknown	6	1.8	3	1.7	3	2.0	

*Statistically significant difference at the $P < 0.05$ level (χ^2 test). [†]UICC stage¹⁷. Stage I, T1N0M0; stage II, T1–3N1M0, T0–2N1M0; stage III, T4N0M0, T3–4N1M0, T0–4N2M0, T0–4N3M0.

for age, as shown in Table 1. On average the FEC group was slightly older with a mean age of 52.6 ($\pm$ SD 9.9) years compared to 50.0 ($\pm$ SD 10.4) years for the non-FEC group ($P = 0.02$).

Tumor pathology

The tumor characteristics are summarized in Table 3. Most of tumors were infiltrating ductal carcinomas of the breast (283/325, 87%) and were high grade (192/325, 59% grade 3). Their hormone receptor status was predominantly positive (73%) as opposed to Her2 overexpression, which was positive in only 21% of patients. Overall 83 percent of patients were IUCC stages II or III. The FEC and non-FEC groups were similar with respect to tumor type, grade, stage and Her2 status. However, in the FEC group 143/176 (81%) tumors were hormone receptor positive, compared to 95/149 (64%) in the non-FEC group ($P < 0.001$).

Chemotherapy

Data concerning the use of different adjuvant chemotherapy regimens are given in Table 4. The most commonly used chemotherapy regimens were FEC100 with no sequential chemotherapeutic agents (95/325, 29%) and doxorubicin with cyclophosphamide (AC, 67/325, 21%). A total of 176 patients (54%) received treatment with FEC, either alone or sequentially with other agents,

compared to 149 patients (46%) in the non-FEC group. In the FEC group 149/176 patients received an epirubicin dose of 100 mg/m² (FEC100, 85%) as opposed to 27 patients who received FEC with an epirubicin dose of 75 mg/m² (FEC75, 15%).

VTE

Overall 54 (17%) patients developed some form of VTE while undergoing chemotherapy, 47 of whom were receiving treatment with FEC (87%). Of the seven who were not receiving FEC three were receiving treatment with AC, two with epirubicin and cyclophosphamide (EC) and two with docetaxel, doxorubicin and cyclophosphamide (TAC).

The overall incidence of VTE was significantly higher in patients who received FEC than those who received another regimen. In the FEC group, 47/176 (27%) patients developed a VTE compared to seven out of 149 patients (5%) in the non-FEC group ($P < 0.001$). Both superficial and deep VTE were statistically more common in patients receiving FEC when analyzed separately (see Table 5). Although numerically there were more superficial than deep VTE in both groups this difference was not statistically significant ($P = 0.52$).

Thirty-six of the 47 (77%) FEC patients developing a VTE had a peripheral venous access device and 11 (23%) had a central venous access device. In the non-FEC group

Table 4 Adjuvant chemotherapy regimens (total $n = 325$) for fluorouracil/epirubicin/cyclophosphamide (FEC) and non-FEC

	FEC			Non-FEC	
	<i>n</i>	% total		<i>n</i>	% total
FEC 100	95	29.2	EC	5	1.5
FEC 75	23	7.1	AC	67	20.6
FEC 100 – docetaxel	31	9.5	AC/EC – taxane	49	15.1
FEC 75 – docetaxel	2	0.6	TAC	20	6.2
FEC 100 – weekly paclitaxel	16	4.9	TAC – paclitaxel	1	0.3
FEC 100 – EC	2	0.6	CMF	3	0.9
FEC 75 – EC	2	0.6	Other	4	1.2
Other [†]	5	1.5			
Subtotal	176	54.2		149	45.8

[†]Other FEC regimens contained FEC 100 only. AC, doxorubicin/cyclophosphamide; CMF, cyclophosphamide/methotrexate/fluorouracil; EC, epirubicin/cyclophosphamide; FEC 75, epirubicin dose 75 mg/m²; FEC 100, epirubicin dose 100 mg/m²; TAC, docetaxel/doxorubicin/cyclophosphamide.

Table 5 Incidence and type of venous thromboembolism for the total cohort ($n = 325$) and within each group (FEC $n = 176$, non-FEC $n = 149$)

		Total		FEC		Non-FEC		<i>P</i>
		<i>n</i>	% total	<i>n</i>	% total	<i>n</i>	% total	
Superficial	SVT Tx arm [†]	22	6.8	20	11.3	2	1.3	<0.001*
	SVT other	1	0.3	1	0.6	–	–	
	STP Tx arm	14	4.3	12	6.8	2	1.3	
	Subtotal	37	11.4	33	18.7	4	2.7	
Deep	DVT Tx arm	10	3.1	7	5.0	3	2.0	0.02*
	DVT other	3	0.9	3	1.7	–	–	
	PE	4	1.2	4	2.3	–	–	
	Subtotal	17	5.2	14	8.0	3	2.0	
Total		54	16.6	47	26.7	7	4.7	<0.001*

*Statistically significant difference at the $P < 0.05$ level (χ^2). DVT, deep vein thrombosis; FEC, fluorouracil/epirubicin/cyclophosphamide; PE, pulmonary embolus; STP, superficial thrombophlebitis; SVT, superficial venous thrombosis; [†]Tx arm, treatment arm.

five of seven patients (71%) had a peripheral device and two (29%) had a central venous access device. There was no significant difference in the incidence of VTE dependent on the type of venous access device.

Of the patients who received FEC followed by a taxane, all VTE occurred during the FEC portion of their treatment. Most thrombotic events occurred during the first three cycles of chemotherapy (46/54, 85%), and were predominantly diagnosed using a Doppler ultrasound (33/54, 61%). Thrombotic events occurred in 28% (41/149) patients who received FEC100 compared with 22% (6/27) patients who received a lower dose of epirubicin (FEC75). This difference was not statistically significant.

In addition to the 54 cases of VTE that occurred during chemotherapy, seven patients had documented

VTE that occurred outside the period of treatment with chemotherapy and were not included in the risk factor analysis. Of these, four patients developed portacath-associated DVT one to 12 months after completing adjuvant chemotherapy. Two of the four patients were being treated with trastuzumab (9 and 12 months post-chemotherapy), another with both trastuzumab and tamoxifen (5 months post-chemotherapy) and one patient on no other targeted therapy (1 month post-chemotherapy). Two further patients developed DVT, one of which progressed, resulting in a PE. The seventh patient developed a DVT following the insertion of a peripherally inserted central catheter line prior to the administration of chemotherapy. No deaths were recorded as a result of VTE.

Risk factors

The use of adjuvant FEC was associated with an increase in the risk of VTE with an OR of 7.9 (95% CI 3.3–19.2, $P < 0.001$). Other risk factors were assessed as either single variables or using multivariate logistic regression to account for the effect of FEC, although none were statistically significant. These included age, BMI, menopausal status, smoking status, past history of venous thrombosis, tumor pathology, grade and stage, hormone receptor status, Her2 status and type of venous access for administering the chemotherapy.

DISCUSSION

The incidence of VTE in this study (17%) was considerably higher than that identified in previous studies involving patients treated with chemotherapy for EBC (1.5–10%)^{9–13} and was comparable to that reported by Goodnough *et al.* for patients with metastatic breast cancer (18%).¹⁸ Many of these EBC studies examined DVT only, which may explain the comparatively low incidence of thrombosis, however a study by Levine *et al.* found that 8.8% of patients treated with adjuvant chemotherapy for stage II breast cancer developed either superficial or deep VTE.¹¹ When considering DVT alone, the incidence of 5% in the current study lies within the range already documented in the literature for patients treated with chemotherapy for EBC.

It is possible our VTE rate was higher than expected due to the inclusion of superficial thrombophlebitis, which is a diagnosis open to clinical interpretation and is not included in other studies. As this causes notable morbidity to patients in terms of local pain and the limitation of cannula sites for subsequent treatments we believe it should be incorporated into prospective studies to accurately assess incidence rates. It is also possible that our clinical suspicion biased our detection in the FEC group and overestimated the results. An analysis of a separate retrospective data set might help assess whether this was the case.

Previous studies have identified a number of risk factors that increase the likelihood of VTE in patients with breast cancer receiving adjuvant chemotherapy. These include the use of hormonal therapy in conjunction with chemotherapy, postmenopausal status, age greater than 50 years, greater body weight, tumor hormone receptor positivity and a history of mastectomy rather than lumpectomy.^{9–11,13} The slightly older age of patients receiving FEC might have played some role in the increased incidence of VTE in the FEC group, but concomitant hormonal therapy was not given and

the type of surgery was not investigated. However, when accounting for the effect of these factors using a logistic regression, the use of FEC was still highly statistically significant in the development of VTE. Similarly, the presence of a central venous catheter had no apparent impact on the development of VTE despite the known risks, and there were no reported cases of arterial thrombosis as described previously.^{19,20}

Although at present there are no studies comparing the incidence of VTE with the use of FEC compared to AC or EC, in a study by von Tempelhoff *et al.* the incidence of VTE in patients receiving EC for EBC was 10%.¹² In the current study only 10 patients received treatment with EC and two developed VTE (20%), whereas 114 patients received AC and only three developed VTE (3%). A small study by Demirkan *et al.* investigated the effect of FEC and EC on fibrinolytic system markers and the D-dimer levels were significantly higher in the FEC group, although they were still within the normal range and none of the patients developed VTE.²¹

Dose escalation of epirubicin from 50 mg/m² to 100 mg/m² in adjuvant FEC has been associated with an increased incidence of acute toxicity including neutropenia, anemia, alopecia, nausea and vomiting.²² In the current study FEC100 was associated with a somewhat higher incidence of VTE compared to FEC75, which may suggest a dose effect of epirubicin in the development of VTE. However, the result was not statistically significant. Given that only 27 patients received FEC75 it is difficult to make any unequivocal conclusion about the nature of this dose relationship, although anecdotal evidence suggests that FEC100 is more of a problem.

The incidence of VTE in patients who received treatment with FEC was significantly higher than in patients who received another type of adjuvant chemotherapy including EC. Most thrombotic complications in the FEC group were superficial venous thromboses. Preclinical research has shown that 5-fluorouracil damages the endothelium, particularly in vessels close to the site of administration rather than systemically, and that this damage may be associated with the development of thrombosis.^{23,24} This may, at least in part, explain the higher incidence of superficial thrombosis in patients receiving FEC. However, due to the small number of thrombotic events in the non-FEC group it was difficult to identify any significant correlation.

The use of 5-fluorouracil has also been shown to reduce the activity of protein C while promoting the activity of fibrinopeptide A, resulting in a pathophysiological picture similar to the activation of coagulation.²⁵ Additionally, 5-fluorouracil is known to increase

platelet aggregation *in vitro*, which may also enhance coagulation.²⁶ Given that FEC was the only adjuvant regimen in the current study that incorporated the use of 5-fluorouracil this raises the possibility that 5-fluorouracil may play a causative role in the pathogenesis of FEC-related VTE. CMF, which also contains 5FU, has previously been shown to be associated with increased risk of VTE.^{10,11,13}

The current study has shown a significant increase in the incidence of VTE with the use of adjuvant FEC compared with other adjuvant regimens in the treatment of EBC, confirming our clinical impression. There is a need for prospective studies to better quantify the problem as well as investigate the pathogenesis, in particular the potential role of 5-fluorouracil and identify means of prevention, or at least risk minimization.

Current recommendations do not support the use of prophylactic anticoagulants in the outpatient setting for either adjuvant or palliative chemotherapy.^{27,28} However, in other specific clinical situations, such as the use of thalidomide or lenalidomide in combination with chemotherapy and dexamethasone in multiple myelomas, a high incidence of VTE was noted and prophylaxis with low molecular weight heparin is now commonplace.²⁹ If it is confirmed that FEC is associated with an excessive risk, then this may need to be considered. In the meantime patient education about the symptoms associated with VTE and increased clinical vigilance is required when treating patients with adjuvant FEC to ensure timely diagnosis and optimal treatment of VTE.

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