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Original Paper

Continuous Infusion of Vincristine, Ifosfamide and Epirubicin over 6 Weeks in Treatment-resistant Advanced Breast Cancer

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28 patients with recurrent advanced breast cancer were treated with a salvage regimen consisting of vincristine, epirubicin and ifosfamide/mesna (VIE). All patients had poor prognostic characteristics defined as relapse within 12 months of chemotherapy or as relapse within a radiotherapy field. Chemotherapy was infused continuously through a central venous catheter using a portable pump. Ifosfamide (3 g/m^2) mixed with mesna (3 g/m^2) was infused for 7 days followed by epirubicin (50 mg/m^2) mixed with vincristine (1.5 mg/m^2) over a further seven days and alternated for a total of 6 weeks. 9 of the 28 patients (32%) responded to VIE (six partial and three complete responses). This included 6 of the 18 patients (33%) who had previously received doxorubicin or mitoxantrone, 6 of the 17 patients (35%) who had an inoperable in-field relapse after radiotherapy for locally advanced cancer, and 5 of the 21 patients (24%) relapsing within 6 months of previous chemotherapy. Median duration of response and overall survival were 3.7 and 6.9 months, respectively. Myelotoxicity was mild. One patient had neutropenic sepsis, 3 patients had grade 3 nausea and vomiting and one patient developed paralytic ileus attributed to vincristine. Central venous catheter complications occurred in 12 of 33 catheters requiring removal in 6. Continuous infusional chemotherapy using vincristine, epirubicin and ifosfamide achieves a 32% overall response rate in treatment-resistant advanced breast cancer, and is associated with minimal toxicity and a short treatment period. VIE may be a suitable alternative to conventional chemotherapy.

Key words: breast cancer, infusional chemotherapy
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INTRODUCTION

VIRTUALLY ALL patients with advanced breast cancer relapse after first-line chemotherapy, and salvage treatment is often considered. However, tumour resistance is prevalent, and response to second- or third-line chemotherapy is uncommon and depends on the patients and agents selected [1, 2]. Delivery of adequate doses of chemotherapy may be impaired by prior treatment affecting the tolerance of normal tissue, most notably the bone marrow. Although the optimum level of dose intensity in breast cancer is not known, it is clear that low doses are less effective than moderately myelotoxic regimens [3], and this compounds the problem of tumour resistance in patients with relapsed disease. There is no effective way of identifying patients with disease sensitive to further chemotherapy. The median survival for patients in second relapse is less than 6 months [1, 2], and patients with resistant disease often receive chemotherapy up to near the time of death because of the temporal difficulties in evaluating the effectiveness of treatment. All these factors combine to reduce the overall benefit that might result from salvage chemotherapy in patients with relapsed advanced breast cancer. Some investigators have attempted to overcome these problems by the use of very high doses of chemotherapy with haemopoietic stem cell rescue. However, the usefulness of this approach is still speculative and the high treatment-related morbidity and mortality, even in experienced centres [4], indicates that this treatment should remain experimental.

Our goal was to design a salvage regimen with moderate dose intensity and acceptable toxicity for patients with relapsed advanced breast cancer. Since there is evidence that interrupted chemotherapy does not impair overall survival when compared to prolonged treatment [5], a regimen with a short overall treatment period was planned in view of the expected limited survival of these patients. A novel continuous infusion regimen was devised to meet these aims, and consisted of moderate doses of epirubicin and vincristine followed by ifosfamide and mesna (VIE), infused continuously on alternate weeks to a total of 6

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weeks. An infusional technique was selected as data indicate a therapeutic advantage for this approach. Hortobagyi and colleagues [6] have shown that epirubicin is more active and less toxic when given by infusion for the treatment of advanced breast cancer. Limited data for vinca alkaloids also indicate a response advantage when administered by continuous infusion [7]. Ifosfamide has proven activity in relapsed breast cancer [8], and toxicity is reduced when given by fractionated dose or by infusion [9]. Ifosfamide also reduces cellular glutathione levels, and increased glutathione levels have been implicated in anthracycline resistance, suggesting possible synergy when these drugs are used in combination [8]. Ifosfamide causes a G2 phase arrest of the cell cycle [10], and there is a theoretical advantage for using a phase specific agent, such as vincristine, after ifosfamide.

PATIENTS AND METHODS

Patients

Patients were eligible if they had histologically confirmed breast cancer, previously treated with at least one regimen for metastatic or locally advanced cancer, or relapsing within 12 months of adjuvant chemotherapy. Prior doxorubicin or mitoxantrone treatment was allowed. Prior radiotherapy was allowed to sites of metastatic or locally advanced disease, providing treatment had been completed at least 4 weeks prior to entry, and there was evidence of progressive disease. Prior or current hormonal therapy was allowed provided there had been no change in therapy 4 weeks prior to VIE. Patients of any age were required to have an ECOG performance value of ≤ 2; creatinine < 150 μmol/l or creatinine clearance > 50 ml/min; serum albumin > 25 g/l, bilirubin < 60 μmol/l, ALT <200 μ/l. Patients were ineligible if they had any psychological or psychiatric illness that would impair the safety of outpatient continuous infusion treatment; or had CNS metastases. The protocol was approved by the Human Research and Ethics Committee of the Western Sydney Area Health Service, NSW, Australia and all patients gave informed consent.

Treatment

A Hickman catheter or a subcutaneously tunnelled Vygon 'nutricath' was inserted into the subclavian vein and chemotherapy was continuously infused with a Pharmacia Deltec CADD-1 ambulatory pump. Patients attended an outpatient clinic each week for toxicity assessment, blood count and change of chemotherapy. Chemotherapy was compounded in approximately 100 ml of normal saline and preloaded into a CADD-1 cassette. Initially, ifosfamide mixed with equidose mesna was infused over 7 days, and followed immediately by an infusion of epirubicin mixed with vincristine over 7 days. These drugs are stable in these conditions [11–15]. Treatment was alternated weekly for a total of 6 weeks (Figure 1). Haemopoietic growth factors were not used.

Dose

The doses of the drugs were determined in a pilot study of 14 previously treated patients with various malignancies [16]. Cohorts of patients were treated at escalating dose levels with the aim of identifying a dose level that could be infused continuously over 6 weeks with minimal dose adjustment or delay. Doses selected for use in pretreated patients were ifosfamide 3 g/m^2 mixed with mesna 3 g/m^2 every 2 weeks and epirubicin 50 mg/m^2 mixed with vincristine 1.5 mg/m^2 on alternate weeks for a total of 6 weeks.

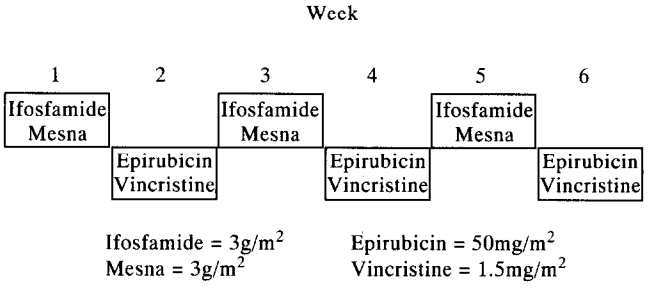

Figure 1. VIE schema. Chemotherapy was given as a continuous infusion over 6 weeks. Ifosfamide mixed with mesna was alternated weekly with epirubicin combined with vincristine.

Dose adjustment

Patients were reviewed at weekly intervals during treatment. If neutrophils were $> 1.5 \times 10^9$/l and platelets $> 100 \times 10^9$/l treatment was continued. If neutrophils were 0.5–1.5 $\times 10^9$/l and/or platelets 50–100 $\times 10^9$/l the infusion rate for the next week was halved to achieve a 50% dose reduction for that week. Treatment was delayed 1 week for values below these levels. For grade 3 non-myelotoxic side-effects other than alopecia or nausea, treatment was delayed until resolution. If there was more than 1 week delay, the patient was removed from the study, but was still assessed for response, toxicity and survival.

Outcome assessment

Response and toxicity were assessed according to WHO criteria. Duration of response, progression-free survival and overall survival were measured from the date of initiation of VIE chemotherapy. Survival and progression-free survival were calculated using the Kaplan–Meier method.

RESULTS

Between July 1991 and June 1992, 28 patients with relapsed advanced breast cancer were entered into the study. Patient characteristics and previous treatment are shown in Table 1, and indicate a group of patients with treatment-resistant disease. All had received previous chemotherapy, and 82% had received radiotherapy to sites of relapse. Seventy-five per cent had relapsed within 6 months or had not responded to previous therapy, and 93% had relapsed within 12 months of previous chemotherapy. 14 patients (50%) had an inoperable in-field relapse after treatment for locally advanced cancers using a protocol consisting of radiotherapy plus a chemotherapy regimen using cyclophosphamide, fluorouracil, methotrexate and mitoxantrone [17]. All patients had progressive disease prior to receiving VIE.

Response

9 of the 28 patients (32%) achieved a response to VIE chemotherapy. 6 patients had a partial response and 3 patients had a complete response. 7 patients (25%) had stable disease and 12 patients (43%) had progressive disease. Treatment was stopped prematurely during VIE treatment due to disease progression in 6 patients and because of toxicity in 1 patient. 21 patients (75%) received at least one complete cycle of VIE chemotherapy. 19 patients received one cycle of VIE and 2 patients received two cycles of VIE concurrently with a 4 week break between cycles. Responses were achieved in skin, lymph nodes, chest wall, bone and lung (lymphangitis). Responses occurred in patients with highly resistant disease; 6 of the 17

Table 1. Patient characteristics

	Median	Range
Age	47	(0–3)
ECOG performance status	1	(32–81)
	No.	(%)
Sites of disease		
chest wall/breast	18	(64)
node	14	(50)
bone	10	(36)
liver	7	(25)
pleural effusion	6	(21)
ascites	3	(11)
skin	3	(11)
lung	2	(7)
lymphangitis	1	
marrow	1	
Previous chemotherapy	28	(100)
1 regimen	8	(29)
2 regimen	15	(54)
3 regimen	4	(14)
4 regimen	1	
doxorubicin or mitoxantrone	18	(64)
Time since previous chemotherapy		
<6 months	21	(75)
6–12 months	5	(18)
>12 months	2	(7)
Relapse in field of previous radiotherapy	23	(82)

(35%) patients who had received prior radiotherapy with or without chemotherapy for locally advanced breast cancer responded in the in-field relapse site; 6 of the 18 (33%) who had received prior mitoxantrone or doxorubicin, and 5 of the 21 (24%) patients who had relapsed within 6 months of prior treatment responded to VIE chemotherapy (Table 2).

Median duration of response was 3.7 months (95% confidence interval 2.8–6.0 months; range 1.2–12 months). Median progression-free survival was 2.9 months (95% confidence interval 2.3–3.7 months; range 1.2–12 months). Median overall survival for the 28 patients was 6.9 months (95% confidence interval 4.1–8.9 months; range 0.5–>25 months).

2 patients received a further cycle of VIE, 1 month after the completion of the initial cycle. Both patients were treated for a chest wall recurrence in the site of previous radiotherapy. One of these patients had a good partial response after the initial VIE cycle and was converted to a complete remission with the second cycle. The second patient had stable disease after the first cycle and was converted to a partial remission with the second cycle.

None of the patients who failed to respond to VIE, responded to subsequent therapy. 4 patients had a further cycle of VIE 2, 3, 9 and 11 months after the initial cycle because of further progression. One patient had a further partial response, 2 had stable disease and 1 progressed on re-treatment with VIE.

Table 2. Response versus time from previous treatment

Time from previous treatment	Number of patients	Response (PR + CR)
<6 months	21	5
6–12 months	5	2
>12 months	2	2
Total	28	9 (32%)

Toxicity

Treatment was generally well tolerated (Table 3). There were no treatment related deaths. Neutropenic fever developed in 1 patient who was inadvertently treated despite being ineligible because of a 4-fold elevation of bilirubin and transaminases above normal due to liver metastases. Myelosuppression was mild with a nadir neutrophil count of $\leq 0.5 \times 10^9$/l occurring in only 1 patient and $\leq 1.0 \times 10^9$/l in 4 patients (Figure 2). 11 patients had a 50% dose reduction during week 5 or 6 because of a neutrophil count of $<1.5 \times 10^9$/l. There was no clinically significant reduction in platelet count. There was a steady fall in haemoglobin and 7 patients required blood transfusion. All of these patients had been recently receiving prior chemotherapy and/or radiotherapy.

Gastrointestinal toxicity was mild. 3 patients had grade 3 nausea lasting for more than 1 week, but the remaining patients had no or minimal nausea. The majority of patients had grade 2 constipation, thought to be related to vincristine infusion and required prophylactic laxatives. One patient developed a paralytic ileus (the same patient who developed neutropenic fever). 3 patients developed grade 2 sensory neuropathy. No other significant cardiac, neurological, renal or urothelial toxicities were associated with VIE chemotherapy.

The VIE regimen was given with minimal dose modification to the majority of patients including those with progressive disease. 11 patients (39%) were treated without dose reduction or delay. 26 patients (93%) had 4 or more weeks of treatment. The received cumulative dose and dose intensity of each cytotoxic agent is shown in Table 4. The majority of patients received >80% of the planned cumulative dose and dose intensity. The mean received dose intensities for epirubicin, vincristine and ifosfamide were 22.3, 0.68, 1470 mg/m^2/week, respectively (planned dose intensity = 25, 0.75, 1500 mg/m^2/week, respectively).

Catheter-related complication rate was relatively high. 2 pati-

Table 3. Toxicity of VIE (n = 28)

	Number of patients
Neutrophils ($\times 10^9$/l)	
1.0–1.5	11
0.5–0.9	4
<0.5	1
Platelets ($\times 10^9$/l)	
<100	1
Haemoglobin (g/dl)	
<10	9
Neutropenic sepsis	1
Nausea	
Grade 0, 1 or 2	25
Grade 3	3
Grade 4	0
Constipation	
Grade 2	19
Grade 3	0
Grade 4	1

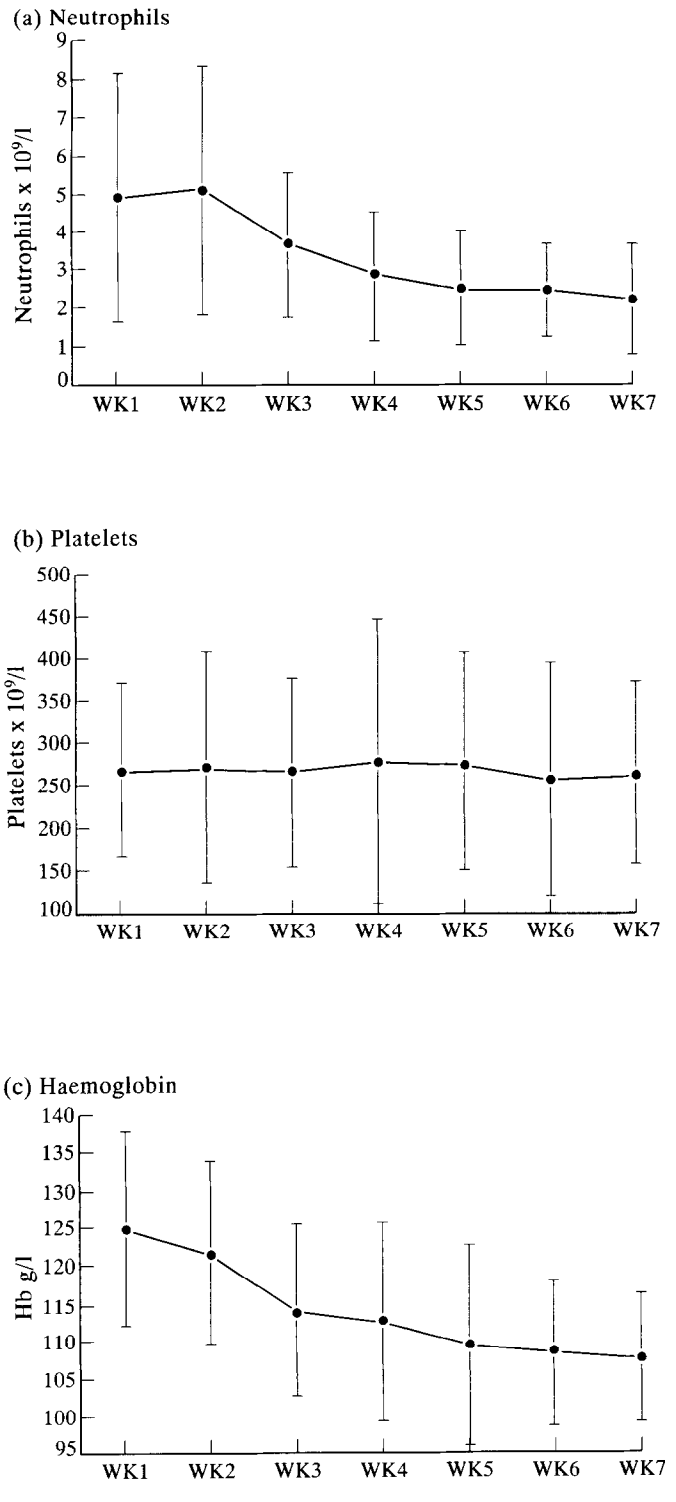

Figure 2. Weekly mean values for 28 patients for neutrophils, platelets and haemoglobin during VIE chemotherapy. Error bars indicate standard deviation.

ents developed a subclavian vein thrombosis. 3 developed a wound or exit site infection and 5 developed a line infection. 1 patient had a definite extravasation of epirubicin with minimal skin toxicity, and another had a possible extravasation with minimal effect. The overall line complication rate was 12/33 (36%) catheters, and led to the removal of six catheters.

Table 4. Received cumulative dose and dose intensity

	No. patients receiving % of planned dose			
	Cumulative dose		Dose intensity	
	80%	100%	80%	100%
Epirubicin/vincristine	19 (68%)	14 (50%)	23 (82%)	16 (75%)
Ifosfamide	23 (82%)	18 (64%)	26 (93%)	21 (57%)

DISCUSSION

While dose of chemotherapy is important, the relative contribution of dose intensity and size, schedule, length of treatment and cumulative dose have not been delineated for most tumours, including breast cancer [3]. No investigator has proven a benefit in departing from the moderate intensity achieved with conventional doses and schedule, and there is evidence of a plateau in the dose–outcome relationship for some tumours [3, 18]. Low dose intensity, although less toxic, gives an unacceptably low response rate [3, 19], and may not give effective palliation. High dose chemotherapy produces higher response rates, but is more toxic, and other benefits such as improved disease-free survival have yet to be shown [4, 20]. Until the role of high dose treatment is defined, other less toxic alternatives need to be investigated, including agents such as the taxanes, or novel methods of using existing chemotherapy, such as that described with the VIE regimen. This regimen offers treatment over a short period at a dose intensity often difficult to achieve with conventional intermittent treatment in pretreated patients, while maintaining a low toxicity profile. The negligible myelotoxicity of this VIE regimen suggests that the doses of epirubicin and ifosfamide may be escalated further without excessive toxicity, particularly in chemotherapy-naive patients.

This study shows that a continuous infusion of epirubicin, vincristine and ifosfamide over a 6 week period is a relatively effective and non-toxic treatment in patients with treatment-resistant advanced breast cancer. The patients in this study had particularly poor prognostic characteristics. Sixty-four per cent of the patients had relapsed after previous doxorubicin or mitoxantrone, 69% had received two or more previous regimens and 82% had received radiotherapy to the site of relapse. Data on salvage therapy for patients who have relapsed after combined chemotherapy and radiotherapy are notably scarce. In the experience of this instution, patients with this pedigree of prior treatment have a particularly poor outcome with salvage treatment, and response to standard therapy has been <10% [17]. Phase II studies for some new drugs, such as paclitaxel and docetaxel [21, 22] report salvage response rates of above 30%. However, the eligibility criteria on these initial studies bias patient accrual, and patients who have relapsed after multiple regimen and radiotherapy are rarely selected. In less selective circumstances, response rates are generally lower. For example, at this institution, response to paclitaxel (175 mg/m^2) was 9% (1 patient) in 11 consecutive patients with similar characteristics to the current study. Responses from salvage therapy for unselected patients in other centres give similar pessimistic results. A preliminary report from Guy's Hospital, London, U.K. reviewed 249 patients who had received two or more chemotherapy regimens, and found a response rate of 16% and median survival of 2.3 months for salvage chemotherapy [23]. A recent

Finnish study reported only one complete response and 18 partial responses in 140 women receiving a median of three salvage therapies after initial relapse from 5-fluorouracil, epirubicin and cyclophosphamide (11% response for all assessable courses) [24]. Median time to treatment failure ranged from 0.5 to 3 months for the various salvage regimens.

The response rate of 32%, progression-free survival of 2.9 months and median length of response of 3.7 months for patients treated with VIE in this study is in keeping with other salvage regimens of longer duration or of greater toxicity [1, 2, 5, 15, 18, 25, 26]. The advantage of VIE over other regimens is tolerability and the short total treatment period. The practical difficulty in offering salvage chemotherapy to patients with such poor prognosis is the uncertainty of response, coupled with the certainty of toxicity of treatment. Patients often progress before an adequate trial of chemotherapy can be given, and dose adjustment is common as a consequence of previous treatment. The clinician is left with the uncertainty as to whether progression was due to absolute tumour resistance or because of the inability to deliver an adequate dose of chemotherapy of a sufficient intensity. VIE is a practical regimen, since all patients receive an "adequate" trial of treatment in a short period, which, therefore, enables selection of patients with sensitive disease who may be suitable for further treatment. Patients who progress during or shortly after 6 weeks of this continuous, moderately, intensive treatment can be identified as having highly resistant disease and unlikely to respond to further standard chemotherapy.

A disadvantage of the VIE regimen is the need for central-line insertion to ensure safety of outpatient infusion of vesicant drugs. Patients in this study had a relatively high catheter-related complication rate. Thrombosis has been reported to occur in over 30% of patients with central line catheters, and usually requires removal, although aggressive anti-thrombolytic therapy may salvage the catheter [27]. In future, patients receiving VIE will receive prophylactic low molecular-weight heparin and, if thrombosis occurs, anti-thrombolytic therapy will be instituted.

VIE is a regimen offering minimal toxicity, a short treatment period and delivers active drugs at a moderate dose intensity to heavily pretreated patients. Response is achieved in a substantial proportion of patients with treatment-resistant breast cancer. These findings suggest that infusional VIE chemotherapy may be a suitable alternative to standard salvage treatment for patients with relapsed advanced breast cancer. Currently, this regimen is being tested at this institution for the treatment of inflammatory breast cancer in conjunction with hyperfractionated radiotherapy. A comparison of VIE with standard intermittent chemotherapy for untreated advanced disease using quality of life as the primary endpoint is also planned.

1. Hortobagyi GN. Salvage chemotherapy for metastatic breast cancer. *Semin Hematol* 1987, **24** (2 suppl 1), 56–61.
2. Buckner JC, Ingle JN, Everson LK, *et al.* Results of salvage hormonal therapy and salvage chemotherapy in women failing adjuvant chemotherapy after mastectomy for breast cancer. *Breast Cancer Res Treat* 1989, **13**, 135–142.
3. Gurney H, Dodwell D, Thatcher N, Tattersal MHN. Escalating drug delivery in cancer chemotherapy: a review of concepts and practice—part 2. *Ann Oncol* 1993, **4**, 103–115.
4. Williams SF, Gilewski T, Mick R, Bitran JD. High-dose consolidation therapy with autologous stem-cell rescue in stage IV breast cancer: follow-up report. *J Clin Oncol* 1992, **10**, 1743–1747.
5. Muss HB, Case D, Richards F, *et al.* Interrupted versus continuous chemotherapy in patients with metastatic breast cancer. *N Engl J Med* 1991, **325**, 1342–1348.
6. Hortobagyi GN, Yap HY, Kau SW, *et al.* A comparative study of doxorubicin and epirubicin in patients with metastatic breast cancer. *Am J Clin Oncol* 1989, **12**, 57–62.
7. Yap YH, Blumenschein GR, Bodey GP, *et al.* Vindesine in the treatment of refractory breast cancer: improvement in therapeutic index with continuous 5-day infusion. *Cancer Treat Rep* 1981, **65**, 775–779.
8. Millward MJ, Harris AL, Cantwell BMJ. Phase II study of doxorubicin and ifosfamide/mesna in patients with advanced breast cancer. *Cancer* 1990, **65**, 2421–2425.
9. Cerny T, Castiglione M, Brunner K, *et al.* Ifosfamide by continuous infusion to prevent encephalopathy. *Lancet* 1990, **335**, 175.
10. Rentschler RE, Barlogie B, Johnston DA, *et al. In vivo* pertubation of human marrow cell cycle progression by ifosfamide. *Cancer Res* 1978, **38**, 2209–2215.
11. Radford JA, Margison JM, Swindell MJ, *et al.* The stability of ifosfamide in aqueous solution and its suitability for continuous 7-day infusion by ambulatory pumps. *Cancer Chemother Pharmacol* 1990, **26**, 144–146.
12. Beijnen JH, Rosing H, de Vries PA, Underberg WJM. Stability of anthracycline antitumour agents in infusional fluids. *J Parenter Sci Technol* 1985, **39**, 220–222.
13. Vendrig DEMM, Beijnen JH, van der Houwen OAGJ, Holthuis JJM. Degradation kinetics of vincristine sulphate and vindesine sulphate in aqueous solution. *Int J Pharm* 1989, **50**, 189–196.
14. Beijnen JH, Neef C, Meuwissen OJAT, *et al.* Stability of intravenous mixtures of doxorubicin and vincristine. *Am J Hosp Pharm* 1986, **43**, 3022–3026.
15. Zhang W, Zalcberg JR, Cosolo W. Interaction of epirubicin with other cytotoxics and anti-emetic drugs. *Anticancer Drugs* 1992, **3**, 593–597.
16. Gurney H, Harnett P, Stuart-Harris R, Kefford R. Phase I study of an outpatient continuous infusion of ifosfamide, mesna, epirubicin, and vincristine. *Proc Clin Oncol Soc Aust* 1991, **18**, 58 (abstr 48).
17. Boyages J, Langlands AO. The efficacy of combined chemotherapy and radiotherapy in advanced non-metastatic breast cancer. *Int J Radiat Oncol Biol Phys* 1987, **14**, 71–78.
18. Gurney H, Dodwell D, Thatcher N, Tattersal MHN. Escalating drug delivery in cancer chemotherapy: a review of concepts and practice—part 1. *Ann Oncol* 1993, **4**, 23–34.
19. Tannock IF, Boyd NF, DeBoer G, *et al.* A randomized trial of two dose levels of cyclophosphamide, methotrexate, and fluorouracil chemotherapy for patients with metastatic breast cancer. *J Clin Oncol* 1988, **6**, 1377–1387.
20. Dunphy FR, Spitzer G, Buzdar AU, *et al.* Treatment of estrogen receptor-negative or hormonally refractory breast cancer with double high-dose chemotherapy intensification and bone marrow support. *J Clin Oncol* 1990, **8**, 1207–1216.
21. Seidman A, Crown J, Reichman B, *et al.* Lack of clinical cross resistance of taxol with anthracycline in the treatment of metastatic breast cancer. *Proc Am Soc Clin Oncol* 1993, **12**, 63 (abstr 53).
22. Valero V, Walters R, Theriault I, *et al.* Phase II study of docetaxol (taxotere) in anthracycline refractory metastatic breast cancer. *Proc Am Soc Clin Oncol* 1994, **13**, 470 (abstr 1636).
23. Gregory WM, Smith P, Richards MA, *et al.* Predicting the response of advanced breast cancer to successive chemotherapy regimens. *Proc Am Soc Clin Oncol* 1993, **12**, 57 (abstr 28).
24. Porkka K, Blomqvist C, Rissanen P, *et al.* Salvage therapies in women who fail to respond to first-line treatment with fluorouracil, epirubicin, and cyclophosphamide for advanced breast cancer. *J Clin Oncol* 1994, **12**, 1639–1647.
25. Hainsworth JD, Andrews MB, Johnson DH, Greco FA. Mitoxantrone, fluorouracil, and high-dose leucovorin: an effective, well tolerated regimen for metastatic breast cancer. *J Clin Oncol* 1991, **9**, 1731–1736.
26. Ahmann FR, Pugh R. Short-term chemotherapy of poor-prognosis metastatic breast cancer with three non-cross resistant chemotherapy regimens: a Southwest Oncology Group Study. *Cancer* 1987, **59**, 239–244.
27. Seigel EL, Jew AC, Delcore R, *et al.* Thrombolytic therapy for catheter-related thrombosis. *Am J Surg* 1993, **166**, 716–719.