Eur J Cancer Clin Oncol, Vol. 23, No. 7, pp. 1079–1080, 1987.
Printed in Great Britain

0277–5379/87$3.00+0.00

Letter to the Editor

A Phase II Study of 4-Deoxydoxorubicin* in Advanced Breast Cancer

ELAINE M. RANKIN,† ROBERT K. KNIGHT and ROBERT D. RUBENS
Imperial Cancer Research Fund, Clinical Oncology Unit, Guy's Hospital, London SE1 9RT, U.K.

4-DEOXYDOXORUBICIN (4DxDx) is an anthracycline which differs from doxorubicin by lacking a hydroxyl group in the 4′-position of the amino sugar. Data from phase 1 trials indicate that 4DxDx may have the most favourable therapeutic index of all anthracycline analogues [1].

We have evaluated 4DxDx as second line treatment in 15 patients with advanced breast cancer who had not previously received anthracyclines. Criteria for entry to the trial were: progressive histologically confirmed breast cancer; age 18–70 years; presence of evaluable disease [2]; white blood count (w.b.c.) $> 4 \times 10^9/\ell$ and platelet count $> 120 \times 10^9/\ell$; adequate liver function (bilirubin < 50 μmd/ℓ and/or aspartate transaminase < 100 u/ℓ) and normal cardiac function including normal baseline left ventricular ejection fraction measured by radionuclide gated angio-cardiography.

4DxDx was give i.v. over 10 min at a dose of 25 mg/m^2 every 3 weeks until the development of progressive disease. If there was no toxicity following the first cycle of treatment the dose was escalated to 30 mg/m^2. If toxicity was experienced the dose was modified as follows: w.b.c. $2–3.9 \times 10^9/\ell$ platelet count $70–119 \times 10^9/\ell$ 50% dose; w.b.c. $< 1.9 \times 10^9/\ell$ platelet count $< 69 \times 10^9/\ell$ treatment postponed for one week. Scalp cooling was not employed and anti-emetics were not routinely given. Toxicity was assessed for each cycle of treatment and graded using the WHO classification [2]. The study parameters, criteria for response and its duration were those published previously [3].

Table 1. Patient characteristics

	No. of patients
Entered	15
Evaluable	14
Median age in years (range) 57 (47–65)	
Reeptor status:	
ER positive	6
ER negative	3
ER unknown	6
Number of previous endocrine treatments	
1	1
2	6
3	5
4	3
Adjuvant chemotherapy with CMF	2
Chemotherapy with CMF for metastatic disease	15
Response to previous CMF	
Complete remission	0
Partial remission	3
No change	4
Progressive disease	8
Site of evaluable disease	
Skin	11
Breast	5
Lymphatic	6
Bone	9
Lung	4
Pleura	3
Liver	4

Details of the 15 patients studied are shown in Table 1. All are evaluable for toxicity and 14 for

Accepted 12 February 1987.
*Supplied by Farmitalia Carlo Erba Ltd.
†To whom correspondence and requests for reprints should be addressed at: Department of Medical Oncology, 1 Horselethill Road, Glasgow, G11 9LX, U.K.

response. One patient died of septicaemia with grade IV marrow toxicity following the second course of treatment before her response could be assessed. All but one patient (who developed cerebral metastases) had at least two cycles of treatment (median 3, range 1–11 cycles). All the patients had received cyclophosphamide, methotrexate and 5-fluoruracil as first line treatment. A total of 51 courses of 4DxDx were given. The dose was escalated in seven cycles and reduced in 15 cycles. Treatment was delayed in one patient because of leukopenia.

One partial remission in the liver lasting 6 months was seen. Three patients achieved stabilization of their disease. Five of the 15 patients were subsequently treated with adriamycin, two achieved a partial response and two a stabilization of their rapidly progressive disease.

Grade 3 nausea and vomiting occured in five patients. Four patients had grade 3 alopecia. Neither mucositis nor phlebitis were seen and extravasation of the drug did not occur. Clinical cardiotoxicity was not seen and there were no changes in the left ventricular ejection fraction in the nine patients (including one who received 245 mg/m^2 4DxDx) in whom it was measured before and after completing treatment. 4DxDx was well tolerated by these patients, many of whom had previously received radiotherapy to marrow bearing areas of bone, and all of whom had previously been treated with combination chemotherapy. Nadir counts were obtained in 10 patients following the first course of treatment. The median w.b.c. was 2.5 (range 1.0–5.4) $\times 10^9/\ell$, the median platelet count 266 (range 133–520) $\times 10^9/\ell$. and the median haemoglobin 11 (range 10.2–12.5) g/ℓ. In one patient after the second course the w.b.c. fell to 0.4 $\times 10^9/\ell$ and the platelet count to 11 $\times 10^9/\ell$. She received intensive supportive care with i.v. antibiotics and platelet transfusion but died of a staphylococcal septicaemia. No other serious toxicity was seen.

A low response rate of 7% was seen. The protocol provided for an escalation of dose depending on the blood count so inadequate treatment is not the cause of the low response rate. No objective responses were seen by Leitner *et al.* in 20 patients, 16 of whom had received prior chemotherapy but none of whom had previously been treated with anthracyclines [4]. It would appear that 4DxDx is not an effective agent for the treatment of advanced breast cancer.

REFERENCES

1. Ferrari L, Rosse A, Brambilla C *et al.* Phase I study with 4′-deoxydoxorubicin. *Invest New Drugs* 1984, **2**, 287–295.
2. *WHO Handbook for Reporting Results of Cancer Treatment.* WHO offset publication No. 48. Geneva, WHO, 1979.
3. Stewart JF, Rubens RD, King RJB *et al.* Contribution of prednisolone to the primary endocrine treatment of advanced breast cancer. *Eur J Cancer Clin Oncol* 1982, **18**, 1307–1314.
4. Leitner SP, Casper EX, Hakes TB *et al.* Phase II trial of 4′-deoxydoxorubicin in patients with advanced breast cancer. *Cancer Treat Rep* 1985, **69**, 1319–1320.