Eur J Cancer Clin Oncol, Vol. 25, No. 1, pp. 141–143, 1989.
Printed in Great Britain

0277–5379/89$3.00 + 0.00

Clinical Trials Summaries

A Phase II Trial of Oral Idarubicin plus Dibromodulcitol in Advanced Breast Cancer

DAVID B. SMITH and ANTHONY HOWELL

Cancer Research Campaign Department of Medical Oncology, Christie Hospital and Holt Radium Institute, Wilmslow Road, Manchester M20 9BX, U.K.

INTRODUCTION

IDARUBICIN is a new anthracycline which demonstrated high potency [1] and low cardiotoxicity [2] in pre-clinical studies. Moreover, it was shown to be active when administered orally [3] and was thus of interest in the treatment of advanced breast cancer where reduced treatment related morbidity has been a major goal over the past few years. A number of phase II trials using single agent idarubicin in patients with advanced breast cancer have shown that this drug has a response rate of 31–40% in previously untreated patients [4–6], results comparable to those obtained with conventional adriamycin regimens [7, 8]. In addition, although gastrointestinal side-effects remain a problem with idarubicin, alopecia is considerably reduced compared with adriamycin. In view of these encouraging results we decided to study idarubicin in combination with another orally active agent, dibromodulcitol [9, 10], in an effort to develop an effective anthracycline based oral regimen.

PATIENTS AND METHODS

Thirty-three evaluable patients with histologically proven breast carcinoma, a WHO performance status of 0–1 and an anticipated life expectancy of at least 3 months were entered into the study. Pleural effusions, ascites, bone disease and lesions in previously irradiated sites were not considered evaluable. Patients with cardiac failure, major rhythm disturbances or significant ECG abnormalities were excluded as were those with a bilirubin greater than 25 mmol/l. Patient characteristics are summarized in Table 1. No patient had received prior chemotherapy but 22 had had one or more trials of endocrine therapy. Reasons for not using endocrine therapy included rapidly advancing and receptor negative tumours.

The distribution of metastatic sites is shown in Table 1. The dominant site of disease was soft

Table 1. Patient characteristics

Characteristic	Number of patients
Total number of patients	33
Age median (range), years	62 (34–87)
Menopausal status:	
Pre	2
Post	31
Previous chemotherapy	0
Previous endocrine therapy	22
Previous radiotherapy	16
Disease sites:	
Lymph nodes	26
Breast	18
Bone	15
Lung	15
Liver	6
Skin	5
Number of involved sites:	
1	4
2	15
3	9
4	5

Accepted 5 September 1988.
Address for correspondence: Dr D.B. Smith, Department of Medical Oncology, Charing Cross Hospital, Fulham Palace Rd, London W6 8RF, U.K.

tissue in 14 patients, visceral in 11 patients and bone in eight patients. Patients with dominant bone disease also had evaluable lesions at other sites.

Response to therapy was assessed according to UICC criteria [11] with duration of remission measured from the date of starting chemotherapy. Liver disease was assessed both clinically and by ultrasound or radioisotope imaging and an overall assessment of bone disease was made using skeletal X-rays and radioisotope scans. Toxicity was graded using the WHO scale [12].

Idarubicin was given in a dose of 45 mg/m^2 and dibromodulcitol in a dose of 500 mg/m^2. The total dose for both drugs was administered in three divided doses on day 1. Treatment was repeated at 21 day intervals and was delayed by 7 days if full haematological recovery had not occurred (total WBC $> 2.9 \times 10^9$/l, platelet count $> 99 \times 10^9$/l).

Patients were reassessed after each course and changed to single agent adriamycin 75 mg/m^2 in a three weekly schedule if there was clear evidence of progression.

RESULTS

The 33 patients received a median of five courses of chemotherapy (range 1–16) and the maximum total dose of idarubicin administered was 600 mg/m^2, with eight patients receiving in excess of 300 mg/m^2. No episodes of cardiac failure or other cardiovascular problems occurred during the study. Gastrointestinal toxicity was mild with grade 1 nausea and vomiting affecting 19 patients and grade 2 six patients. Eight patients (25%) had no gastrointestinal side-effects. Hair loss requiring a wig (grade 3) occurred in three patients and lesser degrees of loss (grades 1–2) in 14 patients.

There were 29 treatment delays in 20 patients as a result of haematological toxicity. On 21 occasions this was due to neutropenia, on three due to thrombocytopenia alone and on five occasions due to both neutropenia and thrombocytopenia. The majority of delays were for 1 week only (20 episodes) but delays of up to 6 weeks occurred after four or five courses had been administered and in these cases it was the platelet count that was slow to recover. There were no episodes of septicaemia during the study, and intravenous antibiotics were not required. At the time retreatment was due grade 1 platelet toxicity was recorded in three patients, grade 2 in three patients, grade 3 in one patient and grade 4 in one patient. No platelet transfusions were required. The patient experiencing grade 4 platelet toxicity had dibromodulcitol omitted from subsequent courses and no further thrombocytopenia was seen. The dose of idarubicin was not reduced. One further patient had a 50% reduction in dibromodulcitol as a result of haematological toxicity. These were the only dose modifications made during the study. Six patients developed a haemoglobin of less than 8 g/dl during treatment and required blood transfusion.

Ten partial remissions were documented providing an objective remission rate of 30.4% (95% confidence interval 15.5–48.7). Partial remissions occurred in patients with the following dominant sites of disease: soft tissue 6, visceral 3 and bone 1. The median duration of remission was 6 months (range 3–12.5+ months). A further five patients had stabilization of disease for a period of at least 6 months.

DISCUSSION

The objective remission rate of 30.4% to the combination of idarubicin + dibromodulcitol in this study was no different to that previously reported for idarubicin alone [4–6]. It appears therefore that dibromodulcitol has contributed little in terms of anti-tumour effect. However, the haematological toxicity was greater in the present study. In trials of single agent idarubicin thrombocytopenia has rarely been a problem whereas with this combination eight patients experienced varying degrees of platelet toxicity resulting in occasional prolonged treatment delays. In addition a significant number of patients required blood transfusions for symptomatic anaemia and although there was no increase in the degree of neutropenia, recovery of the WBC was often delayed until day 28.

The majority of patients treated experienced some degree of gastrointestinal toxicity although in most patients this was of short duration lasting 4–12 hours. Alopecia was the other non-haematological side-effect seen but this was mild with only three patients requiring a wig. This level of non-haematological toxicity is similar to that reported for idarubicin alone and considerably lower than that for adriamycin used in a dose of 50–60 mg/m^2 [7].

This trial used an untried combination in previously untreated patients. Phase II studies are often carried out in heavily pre-treated patients with the result that effective agents may be missed due to the presence of induced drug resistance. A more efficient design, such as that used in this study, would be to administer a phase II drug or combination to untreated patients with provision for early crossover to a 'standard' regimen in the event of obvious treatment failure. Such a protocol would maximize the chance of new effective agents being detected without prejudicing the outlook for individual patients. With the exception of patients with rapidly advancing visceral disease, trial designs of this type would be particularly appropri-

ate in advanced breast cancer where the pace of disease is often slow.

In conclusion, the oral combination of idarubicin + dibromodulcitol resulted in an objective remission rate of 30.4% in 33 patients with advanced breast cancer. This response rate is similar to that reported for single agent idarubicin but haematological toxicity was considerably increased. This combination is not recommended for further study.

Acknowledgements—We thank Farmitalia Carlo Erba Ltd. for supplying idarubicin and Patricia Lobo and Laura Carra for help with data collection.

REFERENCES

1. Suppino R, Necco A, Dasida T *et al.* Relationship between effects on nucleic acid biosynthesis in cell cultures and toxicity of 4-demethoxy derivatives of daunorubicin and adriamycin. *Cancer Res* 1977, **37**, 4523–4524.
2. Bertazzoli C, Bellini O, Magrini U *et al.* Quantitative experimental evaluation of adriamycin cardiotoxicity in the mouse. *Cancer Treat Rep* 1979, **63**, 1877–1883.
3. DiMarco A, Casazza AM, Pratesi G. Antitumour activity of 4-demethoxydaunorubicin administered orally. *Cancer Treat Rep* 1977, **61**, 893.
4. Bastholt L, Dalmark M. Phase II study of idarubicin given orally in the treatment of anthracycline-naive advanced breast cancer patients. *Cancer Treat Rep* 1987, **71**, 451–454.
5. Lionetto RL, Pronzato P, Conte PF, Sertoli MR, Amoroso D, Rosso R. Idarubicin in advanced breast cancer: a phase II study. *Cancer Treat Rep* 1986, **70**, 1439–1440.
6. Pannuti F, Martoni A, Pacciarini MA, Fruet F. A phase II trial of oral idarubicin in advanced breast cancer. *Proc ECCO* 1985, **3**, 70.
7. Brambilla C, Rossi A, Bonfante V *et al.* Phase II study of doxorubicin versus epirubicin in advanced breast cancer. *Cancer Treat Rep* 1986, **70**, 261–266.
8. Hoogstraten B, George SL, Samal B *et al.* Combination chemotherapy and adriamycin in patients with advanced breast cancer. *Cancer* 1976, **38**, 13–20.
9. Andrews MC, Weiss AJ, Wilson W, Nealon T. Phase II study of dibromodulcitol (NSC-104800). *Cancer Chemother Rep* 1974, **58**, 653–660.
10. Mischler NE, Earhart RH, Carr B, Tormey DC. Dibromodulcitol. *Cancer Treat Rev* 1979, **6**, 191–204.
11. Hayward JL, Carbone PP, Heuson J-C, Kumaoka S, Segaloff A. Assessment of response to therapy in advanced breast cancer. *Br J Cancer* 1977, **35**, 292–298.
12. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.