Eur J Cancer Clin Oncol, Vol. 25, No. 2, pp. 357–360, 1989.
Printed in Great Britain

0277–5379/89$3.00 + 0.00

Effective Palliation of Advanced Breast Cancer with Weekly Low Dose Epirubicin

WILLIAM G. JONES

University Department of Radiotherapy, Tunbridge Building, Cookridge Hospital, Leeds LS16 6QB, U.K.

Abstract—*A single institution Phase II study of weekly low dose epirubicin was performed on patients with advanced breast cancer. They received epirubicin in doses approximating to* 12 mg/m^2 *i.v. each week. Most patients had received prior hormone therapy and five had previous chemotherapy; all were post-menopausal. Only patients with bidimensionally measurable visceral or soft tissue metastatic lesions were eligible for objective assessment of response according to WHO criteria. Forty-two patients were evaluable for response and* 46 *were evaluable for toxicity. An objective response rate of* 43% *was observed* (95% *CI* = 27.9–57.8%) *confirming that epirubicin is an active single agent in breast cancer. Remarkably little toxicity was seen;* 35% *of patients reported no toxicity at all. Since this low dose weekly approach was so well tolerated, and yet was effective, useful palliation was achieved in this group of patients.*

INTRODUCTION

ADVANCED BREAST CANCER cannot be cured with cytotoxic drugs, but they can, however, afford useful palliation in the majority of patients with metastatic disease [1]. Unfortunately the associated toxicity commonly affects the quality of the patient's life even though objective disease regression is being observed. Doxorubicin is one of the most useful drugs in the treatment of this condition [2, 3]. In order to overcome the problems of toxicity, many authors have used a lower dose of doxorubicin in a weekly schedule [4–7]. A reduction of toxic effects has been demonstrated while effectiveness has been retained. Epirubicin is one of a series of analogues derived from doxorubicin and is reported to be as effective and less toxic than the parent drug [8]. It is an effective agent in the management of advanced breast cancer with a higher therapeutic index than doxorubicin [9]. Differences in the pharmacokinetics and metabolism of these two drugs may be responsible for the differences in toxicity noticed in early clinical studies [10, 11]. With these facts in mind, a study of the palliative effect of weekly low dose epirubicin therapy in patients with advanced breast cancer was performed.

PATIENTS AND METHODS

Between March 1982 and November 1986, patients with advanced post-menopausal metastatic breast cancer resistant to, or unlikely to respond to, conventional therapy were entered into a Phase II study. Eligibility criteria included: histological proof of breast cancer; ability to adhere to the weekly protocol of therapy; the presence of bidimensionally measurable metastatic soft tissue or visceral lesions, which were used to assess response; the discontinuation of all previous anti-cancer therapies; an initial white cell count $>2 \times 10^9$/l and a platelet count of $>100 \times 10^9$/l. The patients were of any age. Informed consent was obtained before therapy was initiated. Patients with another neoplasm were excluded, as were patients unable to travel to the hospital every week; for example, because of geographical factors. Bone metastases were not used to assess response because of the inability to do this accurately on an objective basis. Radiotherapy given previously or concomitantly was accepted provided this did not interfere with the assessment of response.

The bidimensionally measurable marker lesions were assessed before treatment, then every 4 weeks in accordance with the World Health Organization criteria [12]. All patients had objective evidence of progression of disease at study entry. Treatment was continued only if the patient was responding objectively or held a 'no change' category. Treatment was stopped if the patient showed evidence of progression, or for any other reason if it was in the patients' best interest. Toxicity was assessed from the first day of epirubicin therapy. Treatments such as anti-emetics were not used routinely to prevent toxicity. The patients were questioned weekly and toxicity recorded even if the patient only complained of the effect on one occasion.

Epirubicin was administered weekly either by bolus intravenous (i.v.) injection with saline flush-through or injection into the tubing of a fast running

Accepted 3 October 1988.
Supported by Farmitalia Carlo Erba (U.K.) Limited.

i.v. infusion. A dose of 20 mg/week was used initially on an empirical basis for simplicity, irrespective of the patient's surface area. The doses used in the study varied slightly but approximate to 12 mg/m^2. Weekly treatment was continued for at least 12 weeks provided the patient continued to respond, after which the interval between injections could be increased. A number of relapses were observed between the 16th and 20th weeks on study in these patients, and this led to a change in policy. Responding patients are now encouraged to continue weekly therapy for a minimum of 26 weeks.

Pre-treatment investigations included a complete medical history and physical examination, routine full blood count and biochemistry (including tests of liver function), chest X-ray, ECG and investigations required to assess the size of the measurable lesion(s). Full blood counts and biochemistry were performed weekly. All patients underwent regular chest X-ray and ECG monitoring. Other investigations were performed as dictated by the clinical situation. Assessment of response was undertaken every 4 weeks while the patient remained on study.

RESULTS

Fifty-six patients have been studied. Fourteen were either ineligible or inevaluable for response. Four patients are assessable for toxicity but not response: in one patient there was no histological proof of breast cancer; one patient had no suitable lesions to assess response by; the other two died of tumour after only two courses, assessment of marker lesion response being impossible. Seven patients were given or were continuing potentially active anti-cancer therapy while on study and so were inevaluable. Three other patients were inevaluable; one suffered an early tumour death after only one course, the other two had major protocol violations (wrong drug; wrong dose).

The remainder of this report relates to the 42 fully evaluable patients in terms of the rate and duration of response, and the 46 patients who were evaluable for toxicity. Of the evaluable patients, two were male and 40 were female. The mean age was 61 years (range 41–89 years). The WHO performance status was rather poor with a median of 2 (range 0–3). The dominant sites of metastases were as follows: soft tissue lesions 23 patients (55%), visceral lesion 13 patients (31%), bone lesions six patients (14%). Of course all patients with bone disease also had soft tissue lesions by which response could be assessed, and the majority of patients with mainly soft tissue or visceral also had bone metastases.

All but four of the 42 patients had undergone and failed prior therapy for metastatic disease with hormone manipulation. Five patients had received hormone manipulation followed by adriamycin containing chemotherapy (only one of the latter group responded to therapy). No information was available about the tumour hormone receptor status. Details of prior therapy are given in Table 1. No patient was given adjuvant treatment as part of primary management.

An objective response rate of 43% was seen in the fully evaluable patients (standard error = 7.639, thus 95% confidence interval is 27.9–57.8%). The responses to therapy and duration of response in weeks are shown in Table 2. When a response was observed, this was accompanied by an improvement in performance status in all cases. The duration of responses, as shown in Table 2, is meaningful for this group of patients with far advanced disease. It should be noted that a response was sometimes slow in appearing and if a no change category was pertaining occasionally the patient did eventually achieve a partial response, perhaps after as long as 12 or 14 weeks of therapy. In the early days of the trial, the interval between courses was increased to 2 or 3 weeks after the initial 12 weeks of therapy. This led to a number of relapses within a short period of time. It is now policy to continue with therapy for a minimum of 26 weeks, provided that the patient continues to respond.

The regime was extremely well tolerated, although a few patients did find it inconvenient to attend clinic once a week for the injection. Toxicity was usually very slight and did not occur with every treatment cycle. If a side-effect was reported, it was recorded even if it only occurred during one cycle of therapy. Routine preventative measures were not employed unless the symptom was persistent over a number of couses. Some of the effects reported were probably not treatment related. The effects recorded are shown in Tables 3 and 4. Sixteen patients (35%) reported no toxicity whatsoever.

There was no clinical or ECG evidence of cardiac toxicity in the patients studied. Haematological

Table 1. Prior therapy for metastases

Hormones	
None	4
X-Ray menopause	1
Oophorectomy	1
Androgens	1
Tamoxifen	19
Tamoxifen and prednisolone	2
Tamoxifen and stilboestrol	4
Tamoxifen and progestogens	2
Tamoxifen and androgens	1
Stilboestrol	2
Tamoxifen and aminoglutethimide	1
More than two hormone manipulations	4
Chemotherapy	
None	37
Adriamycin containing combinations	5

Table 2. Duration of responses (weeks)

Response	Number	Duration
CR	0 (0%)	—
PR	18 (43%)	7, 7, 8, 8, 11, 15, 17, 17, 20, 26, 27+, 29, 52, 52, 62, 65, 73, 227+ (Median 20 Mean 40)
NC	20 (48%)	4, 5, 6, 6, 6, 7, 7+, 9, 10, 10, 11, 13, 14, 16, 17, 19, 22, 38, 48, 51 (Median 10 Mean 15)
PROG	4 (10%)	
Total	42 (100%)	

+ indicates continued response; CR = complete response; PR = partial response; NC = no change; PROG = progression.

toxicity was not significant. In an analysis of the data on the first 30 patients, a reduced white cell count below 3×10^9/l was only seen eight times and a count $<2 \times 10^9$/l was seen only once. In those patients receiving 10 or more courses of therapy a WBC of $<2.5 \times 10^9$/l was encountered on only six occasions in a total of 287 courses; five of these were in the same patient. The mean WBC was 5.7×10^9/l. The lowest WBC was 1.8×10^9/l. The lowest platelet count seen was 135×10^9/l and the mean count during the 287 courses was 270×10^9/l. On no occasion was treatment withheld because of a low count. Because of these results, further analysis of haematologic toxicity was not undertaken. Indeed, weekly blood counts have now been abandoned, counts being performed at 3 to 4 weekly intervals only.

DISCUSSION

The palliative therapy of advanced breast cancer has improved with the advent of new hormone and chemotherapeutic agents [1]. It is, however, disturbing for both patient and clinician when toxicity detracts from the quality of survival, while objective disease regression is occuring. A number of studies have been performed showing that low dose weekly doxorubicin therapy is not only feasible but that effectiveness is maintained and toxicity reduced, i.e. the goal of palliation has been achieved [2, 5–7, 13]. Indeed, Gundersen *et al.* have reported a randomized trial comparing combination chemotherapy with vincristine, adriamycin (doxorubicin) and cyclophosphamide on a three weekly basis, against adriamycin 20 mg/week [2]. They conclude that weekly doses of adriamycin as a single agent are as effective as VAC combination with considerably less toxicity. In the present study of low dose weekly epirubicin there was a similar low incidence of toxicity. An objective response rate of 43% (95% CI = 27.9–57.8%) was seen and this compares well with most of the studies of adriamycin therapy reviewed by Perlow and Holland and is better than for other single agents [1].

In the search for palliative treatments which produce a minimal disturbance to normal life style, this facet of low toxicity is important. However, a small number of patients found weekly attendances inconvenient and others found weekly venous cannulation an ordeal. Smith and Howell tried to overcome these problems by giving weekly low dose 4-demethoxydaunorubicin orally [14]. They suggest that the results of giving the same total dose of this drug every 3 weeks is superior and in contrast to weekly adriamycin there is a loss of therapeutic effect when it is given weekly. They also conclude that low dose weekly 4-demethoxydaunorubicin therapy is inadequate for rapidly progressive liver metastases. Aggressive therapy is usually required for these poor prognosis patients. Schwartsmann and Pinedo note that heterogeneity of the disease makes treatment evaluation difficult and that several factors, especially poor performance status and the presence of visceral disease, are associated with a poor response to chemotherapy [15]. On the other hand, such parameters as response to prior hormone

Table 3. Toxicity of therapy (46 patients) (part 1)

Percentage with toxicity	Toxicity	Number with WHO grade 0	1	2
30%	Nausea*	26	14	—
13%	Vomiting		—	6
22%	Alopecia*	36	9	1
11%	Phlebitis*	41	5	—
7%	Diarrhoea*	43	3	—
4%	Stomatitis*	44	2	—
2%	Skin*	45	—	1
2%	Neurotoxicity	45	1	—
0%	Fever	46	—	—

*All these symptoms occurred in one patient on study for only 8 weeks.

Table 4. Toxicity of therapy (46 patients) (part 2)

Toxicity	Number of patients (%)
Lethargy	9 (20%)
Depression	2 (4%)
Dizziness	2 (4%)
Cramps	1 (2%)
Constipation	1 (2%)
Haematological	0 (0%)
Cardiac	0 (9%)
No toxicity reported	16 (35%)

therapy, receptor status, disease free interval and age are not considered relevant to the response rate to chemotherapy in breast cancer [1].

The series reported here could be criticized on the basis of the selection criteria, especially the need for the patients to have bidimensionally measurable soft tissue or visceral lesions by which response could be assessed. No attempt was made to assess response in bone lesions since this is difficult. A 'no change' category for bone lesions is often due to the insensitivity of the criteria of response criteria rather than the effectiveness or otherwise of the therapy [16]. Some would argue that this would lead to response rates which were artificially high, which is why the 95% confidence interval has been calculated. However, most of these patients had advanced life threatening disease, had failed hormone therapy and were in need of palliation. The objective response rate of 43%, the duration of the responses and the low incidence of toxicity (35% reported no toxicity) suggests that effective palliation was achieved in this group of patients by the use of low dose weekly epirubicin. The potential problem of inconvenience for patients and staff caused by weekly attendances is not thought to be large.

Acknowledgements—The author is greatly indebted to Farmitalia Carlo Erba Limited (U.K.) for supplies of the therapeutic agent, and particularly to Miss Pamela Perry and Dr Gwyn Thomas for consistent encouragement and support. Thanks are due to Mrs Anne Pickergill for preparation of the manuscript.

REFERENCES

1. Perlow LS, Holland JF. Chemotherapy of breast cancer. *Med Oncol Tumour Pharmacother* 1984, **1**, 169–192.
2. Gundersen S, Kninnsland S, Klepp O, Kvaløy S, Lund E, Host H. Weekly adriamycin versus VAC in advanced breast cancer. A randomised trial. *Eur J Cancer Clin Oncol* 1986, **22**, 1431–1434.
3. Bonfante V, Ferrar L, Brambilla C *et al.* New anthracycline analogues in advanced breast cancer. *Eur J Cancer Clin Oncol* 1986, **22**, 1379–1385.
4. Chlebowski RT, Paroly WS, Pugh RP *et al.* Adriamycin given as a weekly schedule without a loading course: clinically effective with reduced incidence of cardiotoxicity. *Cancer Treat Rep* 1980, **64**, 47–51.
5. Creech R, Catalano R, Shah M. An effective low-dose adriamycin regimen as secondary chemotherapy for metastatic breast cancer patients. *Cancer* 1980, **46**, 433–437.
6. Mattson W, Borgström S, Landberg T. A weekly schedule of low-dose doxorubicin in treatment of advanced breast cancer. *Clin Ther* 1982, **5**, 193–203.
7. Kessinger A, Lemon HM, Foley JF. Mini-dose weekly adriamycin therapy for patients with advanced malignant disease at increased risk for adriamycin toxicity. *Am J Clin Oncol* 1983, **6**, 113–115.
8. Hurteloup P, Ganzina F. Clinical studies with new anthracyclines: epirubicin, idarubicin, esorubicin. *Drugs Exp Clin Res* 1986, **12**, 233–246.
9. Cersosimo RJ, Hong WK. Epirubicin: a review of the pharmacology, clinical activity and adverse effects of an adriamycin analogue. *J Clin Oncol* 1986, **4**, 425–439.
10. Robert J, Vrignaud P, Nguyen-Ngoc T, Lliadis A, Mauriac L, Hurteloup P. Comparative pharmacokinetics and metabolism of doxorubicin and epirubicin in patients with metastatic breast cancer. *Cancer Treat Rep* 1985, **69**, 633–640.
11. Jain KK, Casper ES, Geller NL *et al.* A prospective randomised comparison of epirubicin and doxorubicin in patients with advanced breast cancer. *J Clin Oncol* 1985, **3**, 818–826.
12. *WHO Handbook for Reporting Results of Cancer Treatment.* WHO Offset Publication No. 48, Geneva, 1979.
13. Scheithauer W, Zielinski C, Ludwig H. Weekly low dose doxorubicin monotherapy in metastatic breast cancer resistant to previous hormonal and cytostatic treatment. *Breast Cancer Res Treat* 1985, **6b**, 89–93.
14. Smith DB, Howell A. A Phase II study of oral weekly 4-demethoxydaunorubicin in advanced breast cancer. *Eur J Cancer Clin Oncol* 1987, **23**, 391–394.
15. Schwartsmann G, Pinedo HM. Clinical trials in advanced breast cancer. *Eur J Cancer Clin Oncol* 1987, **23**, 595–597.
16. Coleman RE, Rubens RD. The clinical course of bone metastases from breast cancer. *Br J Cancer* 1987, **55**, 61–66.