Eur J Cancer Clin Oncol, Vol. 20, No. 5, pp. 631–634, 1984.
Printed in Great Britain.

0277-5379/84$3.00+0.00

Adriamycin and Mitomycin C as Initial Chemotherapy for Advanced Breast Cancer

STEPHANIE A. AMIEL, JOHN F. STEWART, HELENA M. EARL, ROBERT K. KNIGHT and ROBERT D. RUBENS*

Imperial Cancer Research Fund Breast Cancer Unit, Guy's Hospital, London SE1 9RT, U.K.

Abstract—*Adriamycin and mitomycin C in combination have been tested in the treatment of advanced breast cancer. In an initial pilot study 11 heavily pretreated patients received mitomycin C alone and 2 (18%) achieved partial responses. Subsequently, 27 patients who had not received prior chemotherapy for advanced breast cancer were treated with adriamycin 40 mg/m² + mitomycin C 10 mg/m² i.v. every 3 weeks. Six (22%) achieved complete and 10 (37%) achieved partial responses, giving an objective regression frequency of 59%. The median duration of response was 37 weeks (range 8–55+ weeks).*

INTRODUCTION

ADRIAMYCIN remains the most effective single cytotoxic agent currently available for the treatment of advanced breast cancer [1]. There is considerable interest in identifying drugs to combine with adriamycin to give an improved therapeutic regimen. Recent trials of the alkylating agent mitomycin C have demonstrated activity for this drug against breast cancer [2], and this has been confirmed in a pilot study in this unit. Partial responses were observed in two of 11 women with advanced disease treated with mitomycin C 10 mg/m² intravenously once every 3 weeks. The 11 women, aged between 36 and 64 yr, all had progressive disease after prior chemotherapy and so the observed response rate (18%) was of interest. This report describes a trial to test the use of adriamycin and mitomycin C in combination as first-line chemotherapy for patients with advanced carcinoma of the breast.

MATERIALS AND METHODS

Twenty-seven women aged between 33 and 63 yr (mean 47.6 yr) and with progressive metastatic carcinoma of the breast were entered into the trial. None had received chemotherapy as treatment for advanced disease and none had been exposed to the agents under investigation. Four (15%) had presented with advanced breast cancer, but the remainder had had either primary surgery (22 patients) or radiotherapy (5 patients); 11 patients had had primary adjuvant therapy (radiotherapy 7, ovarian ablation 1, chemotherapy 3). Adjuvant chemotherapy had not included adriamycin or mitomycin C. Endocrine treatment had been given for subsequent metastatic disease (ovarian ablation 9, tamoxifen 13, androgens 1, hypophysectomy 2, prednisolone 7). The initial postoperative disease-free interval for these patients ranged between 0 and 72 months (mean 25.8 months) and the time from diagnosis to entry to the trial between 3 and 172 months (mean 49.6 months).

On entry to the study patients underwent physical examination, chest radiograph, haematological and biochemical screens, isotopic bone and liver scans and electrocardiography. Palpable and visible lesions were measured in two perpendicular dimensions and visible lesions were photographed. Areas of increased activity on bone scans were studied by standard skeletal radiography. Only lytic secondary deposits detectable on the radiographs were recorded as baseline lesions. Patients with abnormal cardiac function, abnormal renal function (urea greater than 8 mmol/l), significant liver dysfunction (bilirubin greater than 50 μmol/l; aspartate amino transferase greater than 66 μmol/l) or inadequate bone marrow function (total WBC less than 2000/μl or platelet count less than 70,000/μl) were excluded from the study.

After documentation of baseline lesions patients were treated with adriamycin 40 mg/m² and mitomycin C 10 mg/m² intravenously. Injections

Accepted 7 November 1983.
*To whom requests for reprints should be addressed.

Table 1. Dose modifications according to toxicity

Haematological toxicity grade	White blood cell count (per μl)	Platelet count (per μl)	% dose Adriamycin	% dose Mitomycin C
0	⩾4000	⩾120,000	100	100
1	2000–3999	70,000–119,999	50	50
2	<1999	<69,999	0	0
Hepatic function	Bilirubin (μmol/l)			
	23–50		50	100

were repeated every 3 weeks. Dosage was modified according to residual myelotoxicity (Table 1). The initial dose was similarly reduced for patients with WBC of less than 4000/μl or platelet counts of less than 120,000/μl. All patients were offered scalp cooling as protection against adriamycin-induced alopecia. Twelve patients accepted and underwent scalp cooling for 15 min before and 30 min after each injection (45 min total cooling). Immediately before each injection each patient was questioned about side-effects and was examined. All baseline lesions were measured, visible lesions photographed and a full blood count performed. Baseline radiographs, electrocardiograms and plasma biochemistry were repeated at intervals of 3 months, or earlier if indicated by symptoms.

Response to treatment was assessed according to UICC criteria [3]. Briefly, a partial response was recorded if the sum of the products of the perpendicular axes of the lesions had reduced to 50% or less of the original value and no lesion had progressed or new lesion arisen. A complete response implied resolution of all lesions. Such regressions had to be observed on at least two consecutive occasions to be valid. Progressive disease was indicated by an increase of 25% or more in the sum of the products of the perpendicular axes of the lesions or by the appearance of new lesions. Duration of response was defined from the beginning of treatment to the date of observation of progressive disease.

RESULTS

Twenty-seven patients were entered on the study, with a minimum follow-up of 5 months. One patient died of progressive disease within 2 weeks of her first treatment, but has not been excluded from the analysis.

Objective regression was observed in 16 patients (59%), with six (22%) achieving complete and ten (37%) partial responses. The median duration of response was 37 weeks (range 8–>55), with a median time to treatment failure for all patients of 25 weeks (range 0–>55). There was no significant difference between the duration of response for complete or partial responders (Table 2). Six patients (22%) continue in remission at the time of analysis, of which two are in complete remission.

Table 3 shows the responses according to sites of the metastatic disease. Treatment failure usually occurred in sites affected before treatment. In only six patients did disease develop subsequently in sites previously judged to be disease-free, new lesions occurring in the central nervous system (in three patients), bone (three patients), pericardium (two patients) and liver (one patient).

Fifteen patients (56%) remain alive at the time of analysis, with six (22%) still on the treatment regimen. The medial survival of the whole group is 44.5 weeks (range 2–>74). Survival of responders analysed separately is in excess of 48 weeks (range 24–>74).

Toxicity (Table 4)

Myelosuppression was the major side-effect of the regimen, necessitating dosage reduction in 50% of the 232 courses of therapy, exclusion of mitomycin C from the regimen in four patients (15%) and premature change of therapy in three

Table 2. Duration of response

	Responders		
	All	Complete	Partial
No. of patients (%)	16 (59)	6 (22)	10 (37)
Duration			
Median (weeks)	37	41.5	27*
Range (weeks)	12–>55	12–>55	12–>48
No. in continued remission	6	2	4†

*Complete vs partial, $P = 0.3$, not significant.

†One patient has remained in remission on a subsequent different drug regimen.

Table 3. Objective responses at site of involvement

Site	No. of patients with site involved	No. of patients with* regression at site of initial disease	%*
Breast	11	9(5)	82 (45)
Lymphatic	14	14 (9)	100 (64)
Skin	16	12 (5)	75 (31)
Lung	4	3 (0)	75 (0)
Pleura	7	4 (0)	57 (0)
Skeleton	14	5 (2)	36 (14)
Liver	2	2 (2)	100 (100)

*Complete responses in parentheses.

Table 4. Toxicity

	No. of patients (%)	No. of courses (%)
Total	27	232
White cells		
Grade I	17 (63)	101 (44)
Grade II	3 (11)	5 (2)
Platelets		
Grade I	5 (18)	18 (8)
Grade II	4 (15)	4 (2)
Nausea (moderate and severe)	20 (74)	42 (18)
Vomiting (moderate and severe)	14 (52)	32 (14)
Diarrhoea (moderate)	3 (11)	3 (1)
Stomatitis (moderate and severe)	7 (26)	8 (3)
Local phlebitis	2 (7)	2 (1)
Alopecia:	18 (67)	—
with head cooling ($n = 12$)	3 (25)	—
without head cooling ($n = 15$)	15 (100)	—
Respiratory (see text)	1 (4)	—

(11%). There was one episode of septicaemia, probably related to bone marrow suppression, which responded to supportive treatment.

No patient suffered detectable deterioration of cardiac function. One patient whose ECG was abnormal before chemotherapy discontinued adriamycin at 33 weeks because of an echocardiographic abnormality compatible with mild cardiomyopathy. She was asymptomatic and without physical signs of cardiac disease; no pretreatment sonography was available. No arrhythmias were encountered during treatment.

One patient developed dyspnoea, for which no cause was found. She reponded well to prednisolone and the withdrawal of mitomycin therapy. Lung biopsy was not performed.

Eleven patients have died since entering the study. All these deaths have been attributable to metastatic disease. No death has been attributable to therapy.

DISCUSSION

Adriamycin is probably the most effective single agent available for the chemotherapy of advanced breast cancer. Used as a first-line single chemotherapeutic agent, remission rates of up to 58% have been reported [4, 5], while studies of combinations including adriamycin have been inconclusive. One such regimen gave a remission rate of 48% [6] and another of 61% [7], but others have given rates no different from those achieved by adriamycin alone [8]. We were unable to demonstrate an improved response rate from adding vincristine to adriamycin [5], and the combination showed increased toxicity.

Mitomycin C, described as an alkylating agent over 20 yr ago, was little used because of its severe myelotoxicity. However, more recently a response rate to mitomycin C of 28% was reported in patients with advanced breast cancer [2]. These patients had been heavily pretreated and such a remission rate was considered encouraging. The 18% response rate in our pilot study of single-agent mitomycin C in refractory breast cancer was comparable.

The combination of mitomycin C with adriamycin has now been investigated. Although the response rate of 59% (median duration 37 weeks) reported here is relatively high, it is similar to the rate achieved in this unit for adriamycin

alone [5]. Hence it seems unlikely that the combination of mitomycin C and adriamycin as first chemotherapy for advanced carcinoma of the breast would be shown to be significantly different from the use of adriamycin alone in a prospective randomised trial.

REFERENCES

1. CARTER SK, RUBENS RD. Management of locally advanced and disseminated breast cancer. *Lancet* 1981, **ii**, 795–797.
2. VAN OOSTEROM AT, POWLES TJ, HAMERSMA E, SMITH IE, ENGELSMAN E. A phase II study of mitomycin C in refractory advanced breast cancer. A multicentre pilot study. In: MOURIDSEN HT, PALSHOF T, eds. *Breast Cancer: Experimental and Clinical Aspects*. Oxford, Pergamon Press, 1980, 275–276.
3. HAYWARD JL, CARBONE PP, HEUSON JC, KUMAOKA S, SEGALOFF A, RUBENS RD. Assessment of response to therapy in advanced breast cancer. *Br J Cancer* 1977, **35**, 292–298.
4. HOOGSTRATEN B, GEORGE SL, SAMAL B *et al.* Combination chemotherapy and adriamycin in patients with advanced breast cancer: a Southwest Oncology Group study. *Cancer* 1976, **38**, 13–20.
5. STEINER R, STEWART JF, CANTWELL BMJ, MINTON MJ, KNIGHT RK, RUBENS RD. Adriamycin alone or combined with vincristine in the treatment of advanced breast cancer. *Eur J Cancer Clin Oncol* 1983, **19**, 1043–1052.
6. TRANUM BL, MCDONALD B, THIGPEN T *et al.* Adriamycin combinations in advanced breast cancer. *Cancer* 1982, **49**, 835–839.
7. RUBENS RD, BEGENT RHJ, KNIGHT RK, SEXTON S, HAYWARD JL. Combined cytotoxic and progesterone therapy for advanced breast cancer. *Cancer* 1978, **42**, 1680–1686.
8. RUBENS RD. Breast cancer. In: PINEDO HM. *In Cancer Chemotherapy, The EORTC Cancer Chemotherapy Annual 3*. Amsterdam, Excerpta Medica, 1981, 360–396.
9. WAKAKI S, MARUMO H, TOMIOKA K. Isolation of new fractions of antitumour mitomycins. *Antibiot Chemother* 1958, **8**, 228–240.