Pergamon

European Journal of Cancer, Vol. 33, No. 11, pp. 1893–1895, 1997

Printed in Great Britain
0959-8049/97 $17.00+0.00

PII: S0959-8049(97)00217-7

Short Communication

Paclitaxel by 3-h Infusion and Carboplatin in Anthracycline-resistant Advanced Breast Cancer. A Phase II Study Conducted by the Hellenic Cooperative Oncology Group

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37 patients with advanced breast cancer resistant to anthracyclines were treated with paclitaxel 200 mg/m^2 by 3-h infusion and carboplatin at an area under the curve of 7 mg·min/ml every 4 weeks with G-CSF support. There were 5 (14%, 95% CI 3–25%) complete and 11 (30%, 95% CI 15–45%) partial responders. Median duration of response was 11.5 months (range 5.2–16.8+), median time to progression 8 months (range 0.26–16.8+) and median survival 12 months (range 0.5–19.6+). Grade 3-4 leucopenia (27%), thrombocytopenia (10%) and diarrhoea (5%) were noted. In conclusion, the combination of paclitaxel and carboplatin is active and well tolerated in patients with advanced breast cancer resistant to anthracyclines. © **1997 Published by Elsevier Science Ltd.**

Key words: breast cancer, chemotherapy, paclitaxel, carboplatin
Eur J Cancer, Vol. 33, No. 11, pp. 1893–1895, 1997

INTRODUCTION

PACLITAXEL IS one of the most exciting new anticancer drugs, with impressive clinical activity in several tumour types such as ovarian, breast cancer, lung and head and neck cancer [1]. In a number of clinical trials it has been shown that paclitaxel is definitely active in patients with advanced breast cancer previously treated with anthracyclines with an overall response rate in the range of 30–40% [2–5]. The combination of paclitaxel and cisplatin was reported to be highly effective in patients with advanced breast cancer [6]. Substitution of carboplatin for cisplatin allows the treatment to be given on an outpatient basis, even in patients with compromised cardiac or renal function. Carboplatin has also demonstrated significant activity in untreated patients with advanced breast cancer [7]. Using this information as a background, the Hellenic Cooperative Oncology Group conducted a phase II study of the combination of paclitaxel and carboplatin in patients with advanced breast cancer resistant to anthracyclines.

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Received 28 Jan. 1997; revised 17 Apr. 1997; accepted 18 Apr. 1997. This work has been presented in part at the Breast Cancer Working Conference, Bordeaux, September 1996.

PATIENTS AND METHODS

The eligibility criteria for the present study were: (a) histological proof of advanced breast cancer, (b) measurable or evaluable disease outside pre-irradiated areas, unless a subsequent progression was documented, (c) a performance status (PS) ≤ 2 of the ECOG scale, (d) age ≥ 18 years, (e) previous exposure to an anthracycline or mitoxantrone either in an adjuvant setting (providing that they had relapsed within 12 months of completion of chemotherapy) or for advanced disease (and subsequently progressed), (f) adequate bone marrow, hepatic and renal function, (g) a life expectancy of ≥ 3 months and (h) an informed consent indicating that the patients were aware of the investigational nature of the study. Prior palliative radiotherapy or hormonal therapy was allowed, but this should have been discontinued at least 4 weeks before entering the study.

Pretreatment evaluation included a complete medical history, physical examination, complete blood count (CBC), biochemistry, electrocardiogram, chest X-ray, bone scan, liver ultrasound and CT scan as indicated. CBC and biochemistry were repeated prior to each course of chemotherapy. Examination with imaging techniques was repeated every two cycles. All CT scans and other imaging material pertinent to tumour response to chemotherapy or tumour

progression were reviewed at the end of the study by two of the authors (A. K-F., I.I.).

Paclitaxel was administered at a dose of 200 mg/m^2 by a 3-h infusion followed by carboplatin at an area under the curve (AUC) of 7 mg·min/ml in 30-min infusion at the outpatient clinic. All patients were pretreated with dexamethasone, 20 mg intramuscularly 12 and 6 h before paclitaxel administration, and dimethidene maleate 4 mg and cimetidine 150 mg intravenously 30 min before each treatment. All patients received ondansetron as anti-emetic treatment. G-CSF (filgrastim) at a daily dose of 5 μg/kg subcutaneously was given prophylactically on days 2–12 of each cycle. Treatment was repeated every 4 weeks. Dose modifications of the two drugs have been described in detail previously [8]. Response and toxicity criteria were those adopted from WHO [9]. Duration of response was calculated in the case of a complete response (CR) from the date when the CR was documented until the date of progression and in the case of a partial response (PR) from initiation of treatment with this combination until the date of progression. Time to progression (TTP) and survival were calculated by the Kaplan–Meier method [10]. The present study was a non-randomised phase II study. The initially planned number of participating patients was 30. This sample size allowed us to estimate the expected response rate of 40% with a standard error of 8.3%.

Table 1. Selected patient characteristics (n = 37)

Age (years)		
Median	57	
Range	35–71	
	n	%
Performance status		
0	9	24
1	18	49
2	10	27
Oestrogen receptor (ER) status		
Positive	17	46
Negative	6	16
Unknown	14	38
Menopausal status		
Premenopausal	11	30
Perimenopausal	4	11
Postmenopausal	22	59
Previous adjuvant treatment		
Hormonotherapy	15	41
Chemotherapy	17	46
Anthracycline-containing	6	16
Mitoxantrone-containing	5	14
Previous treatment for advanced disease		
Hormonotherapy	16	43
Chemotherapy	32	86
Anthracycline-containing	30	81
Mitoxantrone-containing	2	5
Number of metastatic sites		
1	11	30
2	12	32
≥3	14	38
Metastatic sites		
Locoregional	14	38
Axillary nodes	6	16
Skin	6	16
Residual breast	3	8
Supraclavicular nodes	7	19
Distant	34	92
Bones	12	32
Lung	13	35
Liver	21	57
Nodes	8	22
Skin	8	22
Other breast	1	3
Visceral metastases	25	68

RESULTS

From September 1994 until June 1996, 37 patients, from four participating centres, entered this study. Selected patient characteristics are shown in Table 1.

Analysis of the results in the present study was performed on the 'intention to treat' basis and therefore all registered patients were considered evaluable for response, toxicity and survival analysis.

Overall, 16 patients (43%, 95% CI 27–60%) responded, 5 (14%, 95% CI 3–25%) with CR and 11 (30%, 95% CI 15–45%) with a PR. Responses were seen in all metastatic sites.

As of June 1996, after a median follow-up of 11.4 months, 27 patients (73%) had tumour progression and 20 (54%) had died. Median duration of response was 11.5 months (range 5.2–16.8+), median duration of CR 7.5 months (range 6.5–16.8+), median TTP 8 months (range 0.26–16.8+) and median survival 12 months (range 0.5–19.6+).

In 14 patients (38%), treatment was discontinued before the sixth cycle due to progression of the disease (12 patients) or toxicity (2 patients). In these 2 patients, one developed after the third cycle sensory disturbances and flaccid tetraparesis with reduced muscle tone and tendon reflexes without pyramidal signs, whilst the other patient suffered irreversible cardiac failure after the first cycle of treatment. She had received doxorubicin 90 mg/m^2 and radiation to the chest wall for advanced disease, but that treatment was discontinued because of tumour progression 2 months before the initiation of paclitaxel and carboplatin chemotherapy. A total of 190 cycles were administered, 135 (71%) at full dose and 176 (93%) on schedule. The median dose intensity of paclitaxel actually delivered was 48.9 mg/m^2/week and the relative dose intensity 0.98. The median dose of carboplatin at the first cycle was 389 mg/m^2 (range 167–530). The incidence of various side-effects is depicted in Table 2.

DISCUSSION

In this paper we report our experience with the combination of paclitaxel and carboplatin in anthracycline-resistant advanced breast cancer. There is an increasing body of

Table 2. Incidence (%) of various side-effects

Toxicity	Grade				
	0	1	2	3	4
Anaemia	65	16	16	3	0
Leucopenia	59	3	11	16	11
Thrombocytopenia	71	5	14	5	5
Nausea/vomiting	57	24	19	0	0
Diarrhoea	87	0	8	5	0
Infection	86	11	0	3	0
Neuropathy	40	27	30	0	3
Arthralgias/myalgias	48	44	8	0	0
Mucositis	86	3	8	3	0
Cardiac	97	0	0	0	3

Alopecia was universal.

evidence that paclitaxel, one of the most promising new agents in the treatment of breast cancer, demonstrates significant activity in patients with advanced breast cancer resistant to anthracyclines. Clinical studies indicate that response rates to paclitaxel are similar in women sensitive or resistant to anthracyclines [1, 2].

Recently, there has been an increasing interest in combining paclitaxel with cisplatin. The activity of this combination in ovarian cancer [11] makes it an attractive regimen for the treatment of other malignancies. In advanced breast cancer, Wasserheit and associates [12] reported that the response rate of the combination of paclitaxel 200 mg/m^2 over 24 h followed by cisplatin 75 mg/m^2 and G-CSF support was 48%. In the present study, using the same dose level of paclitaxel, but in 3-h infusion, followed by carboplatin, instead of cisplatin, we obtained similar results. Although it has been demonstrated by our group and others that this combination is active in a variety of cancers, such as ovarian cancer [13], non-small cell lung cancer [14, 15] and head and neck cancer [9], to our knowledge this is the first report on the activity of this regimen in advanced breast cancer resistant to anthracyclines. It is noteworthy that the response rate achieved with this combination is not superior to that reported with paclitaxel alone in this patient population [2, 4]. However, definite conclusions cannot be drawn from small-size phase II studies and, at present, data from randomised studies are lacking.

Toxicity from chemotherapy in the present study was generally manageable. Due to the prophylactic use of G-CSF, the incidence of severe leucopenia was only 27%, while at the same time the dose intensity of both drugs was sufficiently maintained. Reduced morbidity represents a major contribution to the improvement of the quality of life of these patients, given the palliative nature of these treatments. However, we have to keep in mind that the treatment cost increases substantially with G-CSF. This necessitates the performance of well-designed cost-effectiveness analyses before this type of expensive treatment could be recommended outside of a clinical protocol.

In conclusion, the present study clearly shows that the combination of paclitaxel and carboplatin is active and well tolerated in advanced breast cancer resistant to anthracyclines. Currently, we are exploring the role of this combination as first-line chemotherapy in patients with advanced breast cancer.

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