Eur J Cancer, Vol. 29A, No. 12, pp. 1729–1731, 1993.
Printed in Great Britain

0959–8049/93 $6.00 + 0.00

Phase I Study of Epirubicin Plus Vinorelbine With or Without G-CSF in Advanced Non-small Cell Lung Cancer

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The present phase I study was designed to determine the maximum tolerated dose (MTD) of epirubicin, administered every 3 weeks to patients with advanced non-small cell lung cancer (NSCLC), and combined with a conventional dose of vinorelbine [25 mg/m² intravenously (i.v.) days 1 and 8] with or without the support of granulocyte-colony stimulating factor (G-CSF). 18 patients entered the study. The patients received the following four dose levels of epirubicin (i.v., day 1): 50 mg/m² (3 patients) and 60 mg/m² (6 patients) without G-CSF, 75 mg/m² (3 patients) and 90 mg/m² (6 patients) with G-CSF (5 μg/kg days 4–6 and 9–15). In the patients treated without G-CSF the MTD of epirubicin was 60 mg/m² and leukopenia was the dose-limiting toxicity. In the patients treated with G-CSF the MTD was 90 mg/m², myelotoxicity being the dose-limiting toxicity. We observed 1/3 partial response (PR) with epirubicin at the dose of 75 mg/m² and 2/6 PR at 90 mg/m². These results would indicate the usefulness of a phase II study with epirubicin at the dose of 90 mg/m² in association with conventional dose of vinorelbine with the support of G-CSF in advanced NSCLC.
Eur J Cancer, Vol. 29A, No. 12, pp. 1729–1731, 1993.

INTRODUCTION

EPIRUBICIN IS a doxorubicin analogue with less toxicity than its parent drug and a similar spectrum of action [1]. Epirubicin, like doxorubicin, has shown limited activity in non-small cell lung cancer (NSCLC) when used at standard doses [2–5]. Recent studies suggest that high dose epirubicin (120–135 mg/m²) may have higher antitumour activity than standard dose in patients with NSCLC with 21–56% objective response (OR) [6–10]. Myelosuppression was the most important side-effect and leukopenia was dose-limiting toxicity. Vinorelbine is a new vinca alkaloid with high activity in the treatment of NSCLC with 29–32% OR [11, 12]. The aim of this phase I study was to determine the maximum tolerated dose (MTD) of epirubicin, administered every 3 weeks, in patients with stage IIIB-IV NSCLC, when given in association with conventional dose of vinorelbine with or without the support of granulocyte-colony stimulating factor (G-CSF).

MATERIALS AND METHODS

Eligibility criteria included histologically proven stage IIIB-IV NSCLC, performance status (ECOG) 2 or less, age 70 years or less, no previous chemotherapy, white blood cells (WBC) $> 4000/mm^3$, platelets $> 120000/mm^3$, bilirubin ≤ 1 mg/100 ml, creatinine ≤ 1.2 mg/100 ml, normal cardiac, hepatic and renal functions. All patients were staged with cranial, thoracic and abdominal computer tomography (CT) scan and bone scan. Blood count, biochemical tests and electrocardiogram (ECG) were carried out at entry and before each subsequent course. Interim blood counts were carried out twice a week during the treatment. Radionuclide angiocardiography at rest with evaluation of the left ventricular ejection fraction (LVEF) was obtained at baseline conditions and after every two cycles of therapy. Vinorelbine was administered at the conventional dose of 25 mg/m² intravenously (i.v.) days 1 and 8. Epirubicin dose was escalated progressively in groups of ≥ 3 patients. 3 patients entered the starting dose level. If 1 of 3 patients treated with a given dose level experienced grade 3 or 4 toxicity, except hair loss, 3 additional patients entered at that level. We considered the MTD as the dose which caused myelotoxicity grade 3 in 50% of cases and/or grade 4 in 20% of cases. From January to September 1992, 18 patients entered the study. They received four dose levels of epirubicin (i.v., day 1): 50 mg/m² (3 patients) and 60 mg/m² (6 patients) without G-CSF, 75 mg/m² (3 patients) and 90 mg/m² (6 patients) with G-CSF. G-CSF was administered at the dose of 5 μg/kg per day, subcutaneously on days 4, 5, 6 and 9, 10, 11, 12, 13, 14, 15 of each chemotherapy course. The cycle of chemotherapy was repeated every 21 days. Therapy was continued for a maximum of six cycles in patients who achieved an OR. No escalation of the initial dose was planned in any case. Evaluation of response and toxicity were graded according to WHO criteria [13]. Characteristics of patients are reported in Table 1.

RESULTS

In the patients treated with chemotherapy without G-CSF haematological toxicity was exclusively observed on granulocytes. With epirubicin at 60 mg/m² we observed neutropenia grade 3 in 4 patients, and grade 4 in 1 patient with one septic complication requiring hospitalisation, 1 patient had thrombocytopenia of grade 2 and anaemia of grade 3. Nausea and vomiting never exceeded grade 2. The MTD of epirubicin without G-CSF was established at 60 mg/m² and leukopenia was

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Received 6 Apr. 1993; accepted 8 Apr. 1993.

the dose-limiting toxicity. In patients treated with G-CSF and epirubicin at 90 mg/m^2 we observed a case of grade 2 neutropenia, 2 cases of grade 3 thrombocytopenia, 1 case of grade 2 and 1 case of grade 3 anaemia. In 2 patients chemotherapy was delayed because of myelotoxicity with haemoglobin = 7 g/100 ml in a case and platelets = 70 000/mm^3 in the other case at day 21. Nausea and vomiting never exceeded grade 2. There were 2 patients who developed grade 2 mucositis. Local tolerance was acceptable and all treatments were administered without a central venous access. No patient had cardiotoxicity. The MTD of epirubicin with G-CSF was established at 90 mg/m^2 and myelotoxicity, grade 3 thrombocytopenia in 2 cases and grade 3 anaemia in 1 case, was dose-limiting. Table 2 summarises the toxicity data reporting the highest degree of toxicity observed during the study. In the patients treated with epirubicin at 50 mg/m^2 and 60 mg/m^2 no OR was observed. A PR with epirubicin at 75 mg/m^2 and 2 PR at 90 mg/m^2 were reported.

DISCUSSION

Non-small cell lung cancer includes a group of poorly drug-responsive tumours. Cisplatin (CDDP)-based chemotherapy regimens have been widely used in the advanced disease. Combinations containing CDDP, mitomycin C and vindesine or vinblastine have been reported to yield the highest response rates [14]. In recent studies high dose epirubicin showed high activity and moderate toxicity in NSCLC [6–10], contrary to previous poor results using lower doses [2–5]. In two different studies Wils and Martoni using epirubicin at the dose of 120–165 mg/m^2 and 135–150 mg/m^2, respectively, obtained 25% OR [7, 8]. Smit *et al.* treated 25 patients with 135–150 mg/m^2 epirubicin, reporting 36% OR [9]. The best results have been obtained in 24 patients by Villar *et al.* with 56% OR, using epirubicin at the dose of 150 mg/m^2 [10]. In the light of these interesting results reported with high dose epirubicin [6–10] and the appreciable antitumour activity showed by vinorelbine [11, 12] in NSCLC, the present study was designed to determine the MTD of epirubicin when associated with vinorelbine at conventional dose and possibly to develop an effective non-cisplatin-containing chemotherapeutic regimen for the treatment of NSCLC. In the patients treated with chemotherapy without G-CSF the MTD of epirubicin was found to be 60 mg/m^2 and leukopenia was the dose-limiting toxicity. Therefore, we continued the process of dose-finding of epirubicin with the support of G-CSF. G-CSF is a haematopoietic growth factor that promotes the proliferation and differentiation of neutrophils and reduces chemotherapy-related neutropenia in cancer patients [14]. With G-CSF the MTD of epirubicin was established at 90 mg/m^2 and myelotoxicity was the dose-limiting toxicity. We observed 1 PR with epirubicin at the dose of 75 mg/m^2 and 2 PR at 90 mg/m^2. These results would indicate the usefulness of a phase II study with epirubicin at the dose of 90 mg/m^2 plus vinorelbine at conventional dose with the support of G-CSF in advanced NSCLC.

Table 1. Characteristics of patients

No. of patients	18
Sex	
Male	16
Female	2
Age	
Median	64
Range	(52–69)
Performance status	
0	3
1	7
2	8
Stage	
IIIB	4
IV	14
Histology	
Epidermoid	10
Adenocarcinoma	7
Large cell	1

Table 2. Toxicity

	Dose (mg/m^2) with G-CSF			
Side-effects (WHO grade)	50 (n=3)	60 (n=6)	75 (n=3)	90 (n=6)
Neutropenia				
1	2	2	2	0
2	1	0	1	1
3	0	3	0	0
4	0	1	0	0
Leukopenia				
1	0	1	1	0
2	3	1	0	1
3	0	2	0	0
4	0	2	0	0
Infections				
1	0	0	0	0
2	0	0	0	0
3	0	1	0	0
4	0	0	0	0
Thrombocytopenia				
1	0	0	0	2
2	0	1	2	0
3	0	0	0	2
4	0	0	0	0
Anaemia				
1	2	2	1	1
2	1	0	0	1
3	0	0	0	1
4	0	0	0	0
Nausea/vomiting				
1	2	3	1	1
2	1	0	2	2
3	0	0	0	0
4	0	0	0	0
Mucositis				
2	0	0	1	2
3	0	0	0	0
4	0	0	0	0
Alopecia				
1	0	1	0	0
2	3	3	1	2
3	1	2	2	4

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Eur J Cancer, Vol. 29A, No. 12, pp. 1731–1734, 1993.
Printed in Great Britain

0959–8049/93 $6.00 + 0.00

Prognostic Value of Quality of Life Scores in a Trial of Chemotherapy With or Without Interferon in Patients with Metastatic Malignant Melanoma

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In a multi-centre randomised clinical trial comparing dacarbazine (DTIC) plus recombinant interferon-alfa2a (IFN) versus DTIC alone for patients with metastatic malignant melanoma, aspects of quality of life (QL) were measured prospectively by patients using linear analogue self assessment (LASA) scales including the GLQ-8 and by doctors using Spitzer's QL Index. QL scores and performance status at the time of randomisation were available for 152 of 170 eligible patients. These scores carried significant prognostic information. In univariate analyses, Spitzer QL Index assessed by the doctor and LASA scores for physical wellbeing (PWB), mood, pain, appetite, nausea and vomiting, GLQ-8 total and overall QL were significant ($P < 0.01$) predictors of subsequent survival. QL Index and LASA scales for mood, appetite, and overall QL remained independently significant (all $P < 0.05$) in multivariate models allowing for significant prognostic factors other than QL (liver metastases and performance status). These findings closely parallel those in patients with metastatic breast cancer. They add further validity to the QL Index and LASA scores, provide the first evidence of the prognostic significance of the GLQ-8, and argue strongly for the routine assessment of QL in future therapy trials.
Eur J Cancer, Vol. 29A, No. 12, pp. 1731–1734, 1993.

INTRODUCTION

QUALITY OF LIFE (QL) is an important consideration during management of patients with metastatic malignant melanoma. Over recent years, several methods have been developed which allow reliable and valid measurement of aspects of QL affected by advanced malignancy and its treatment [1–6]. Such measures have usually been used to compare different treatments [1, 4, 7], though prognostic associations with QL scores have been reported in breast cancer [1, 8, 9] and lung cancer [10]. We now describe the prognostic associations of QL scores obtained during a multicentre randomised clinical trial comparing dacarbazine (DTIC) plus recombinant interferon-alfa2a (IFN) versus DTIC alone for patients with metastatic malignant melanoma.

PATIENTS AND METHODS

Full details of the clinical trial on which this study is based are presented elsewhere [11]. Briefly, ambulant patients with measurable metastatic melanoma unsuitable for local therapy, who had adequate liver, marrow and renal function were randomised to receive DTIC 800 mg/m^2 every 3 weeks with or