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CLINICAL TRIAL REPORT

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Phase I study of ifosfamide plus high-dose epirubicin in advanced non-small-cell lung cancer

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Abstract The present phase I study was designed to determine the maximum tolerated dose (MTD) of epirubicin given in combination with ifosfamide at a dose of 3 g/m^2, recycled every 4 weeks, in patients with advanced non-small-cell lung cancer (NSCLC). A total of 18 patients entered the study; they received the following four dose levels of epirubicin (i.v., day 1): 75 (6 patients), 90 (3 patients), 105 (3 patients), and 120 mg/m^2 (6 patients). The MTD of epirubicin was 120 mg/m^2, neutropenia being the dose-limiting toxicity. We observed 1/6, 1/3 1/3, and 2/6 partial responses (PRs) at epirubicin dose levels of 75, 90, 104, and 120 mg/m^2, respectively. A phase II study of epirubicin given at a dose of 120 mg/m^2 in association with conventional-dose ifosfamide in advanced NSCLC is in order.

Key words Chemotherapy · NSCLC · Epirubicin · Ifosfamide

Introduction

Epirubicin is a less toxic analogue of doxorubicin, although its spectrum of action is similar. Similar to doxorubicin, standard-dose epirubicin has shown limited activity in non-small-cell lung cancer (NSCLC) [7, 12]. Recent studies have shown that in patients with NSCLC, high-dose epirubicin (120–135 mg/m^2) has increased antitumor activity as compared with the standard-dose regimen, with objective responses (ORs) ranging from 21% to 56% [3, 10, 13, 16, 17]. Ifosfamide is active against NSCLC, with 15–30% ORs being reported [2]. The aim of this phase I study in patients with stage IIIB–IV NSCLC was to determine the maximum tolerated dose (MTD) of epirubicin given in association with a conventional dose of ifosfamide.

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Patients and methods

Eligibility criteria included histologically proven stage IIIB–IV NSCLC, an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2, an age of ≤70 years, no previous chemotherapy, a WBC of >4,000/mm^3, a platelet count of >120,000/mm^3, a bilirubin level of ≤1 mg/100 ml, a creatinine value of ≤1.2 mg/100 ml, and normal cardiac, hepatic, and renal function. All patients were staged with cranial, thoracic, and abdominal computed tomography (CT) scans. Blood counts, biochemistry tests, and electrocardiograms (ECGs) 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 and after every two cycles of therapy.

Ifosfamide was given i.v. at the conventional dose of 3 g/m^2 on day 1. The epirubicin dose was escalated progressively in groups of at least three patients. Three patients were entered at the starting dose level. If one of three patients treated at a given dose level experienced any grade 3 or 4 toxicity except hair loss, three additional patients were treated at that dose level. We considered the MTD as the dose that caused myelotoxicity of grade 3 in 50% of cases and/or of grade 4 in 20% of cases. From October 1993 to October 1994, 18 patients entered the study, including 16 men and 2 women. The median age was 59.5 (range, 45–69) years. The performance status was 0 in one case, 1 in ten cases, and 2 in seven cases. In all, 6 patients had stage IIIB disease and 12, stage IV disease. The histology was epidermoid in 6 cases, adenocarcinoma in 11 cases, and large-cell carcinoma in 1 case. The 18 patients received 4 dose levels of epirubicin (i.v., day 1): 75 (6 patients), 90 (3 patients), 105 (3 patients), and 120 mg/m^2 (6 patients). The cycle of chemotherapy was repeated every 28 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. Responses and toxicity were graded according to WHO criteria.

Results

In the group treated with 75 mg/m² epirubicin we observed grade 1 neutropenia in two patients and grade 4 neutropenia in one patient, with one septic complication requiring hospitalization. One patient had grade 2 thrombocytopenia and two patients had grade 2 anemia. In patients treated with epirubicin at a dose of 90 mg/m² and then at a dose of 105 mg/m², toxicity never exceeded grade 2. At the dose level of 120 mg/m² we observed grade 2 neutropenia in two patients and grade 2 neutropenia in three patients; two patients had grade 2 thrombocytopenia and two patients had grade 2 anemia. In one patient, chemotherapy was delayed by 1 week because of neutropenia on day 28. Nausea and vomiting never exceeded grade 2. No patient showed cardiotoxicity. The MTD of epirubicin was established at 120 mg/m² and myelotoxicity (grade 3 neutropenia) in three cases was the dose-limiting toxicity. The toxicity data involving the highest degree of toxicity observed during the study are shown in Table 1.

One partial response (PR) was observed in each of the three groups of patients treated with epirubicin at either 75 or 90 mg/m² or 105 mg/m², lasting for 2.4 and 3 months, respectively. Two PRs in patients given epirubicin at 120 mg/m² were observed; the duration of response at 120 mg/m² was 4 and 5 months, respectively.

Table 1 Toxicity of ifosfamide plus high-dose epirubicin in advanced NSCLC

Side effects (WHO grade)	Dose (mg/m²) 75 (*n* = 6)	90 (*n* = 3)	105 (*n* = 3)	120 (*n* = 6)
Neutropenia				
1	2	2	2	1
2	0	0	1	2
3	0	0	0	3
4	1	0	0	0
Leukopenia				
1	2	2	2	1
2	0	0	1	3
3	0	0	0	2
4	1	0	0	0
Infections				
1	0	0	0	0
2	0	0	0	0
3	1	0	0	0
4	0	0	0	0
Thrombocytopenia				
1	0	0	1	0
2	1	0	0	2
3	0	0	0	0
4	0	0	0	0
Anemia				
1	0	0	1	0
2	2	0	0	2
3	0	0	0	0
4	0	0	0	0
Nausea/vomiting				
1	2	1	1	1
2	1	0	0	1
3	0	0	0	0
4	0	0	0	0
Mucositis				
1	0	1	0	1
2	0	0	1	2
3	0	0	0	0
4	0	0	0	0
Alopecia				
1	0	0	0	0
2	2	0	1	2
3	4	3	2	4

Discussion

NSCLC is a tumor scarcely responsive to drugs. Chemotherapy including cisplatin (CDDP) has been widely used in advanced cases. CDDP-based regimens containing mitomycin C and vinca alkaloids or ifosfamide induce the highest response rates [1]. Among non-CDDP-based regimens, combinations including mitomycin C and vindesine are associated with the best results [5, 9]. High-dose epirubicin has shown increased activity in NSCLC [3, 10, 13, 16, 17] as compared with the disappointing results achieved with standard doses [7, 12]. Wils et al. [17] and Martoni et al. [10] used epirubicin at 120–165 and 135–150 mg/m², respectively, and both reported 25% ORs. Using a dose of 150 mg/m², Villar et al. [16] obtained ORs in 56% of patients. Ifosfamide is one of the most active drugs in NSCLC, showing 15–30% ORs [2]. It has been included in the most widely used and effective chemotherapeutic regimens in NSCLC, such as CDDP plus mitomycin C plus ifosfamide [1] and CDDP plus vinblastine plus ifosfamide [8], yielding a response rate of about 40%. Although phase I or II studies of high-dose epirubicin plus cisplatin or VP-16 or vinorelbine have been performed in NSCLC, data have not been reported on the association of high-dose epirubicin with ifosfamide [6, 11, 14].

In view of the interesting results obtained with high-dose epirubicin [3, 10, 13, 16, 17] and the antitumor activity of ifosfamide [2] in NSCLC, the present study was designed to determine the MTD of epirubicin in association with ifosfamide given at a conventional dose (3 g/m²) [1, 8] and, possibly, to develop an effective non-CDDP-containing regimen for NSCLC. Phase I studies of ifosfamide plus epirubicin given at escalating doses in soft-tissue sarcoma have been performed [4, 15]. However NSCLC patients represent a different population due to their generally greater age and associated smoking-related disease, namely, respiratory and cardiovascular diseases. In our study the MTD of epirubicin was found to be 120 mg/m² and neutropenia was the dose-limiting toxicity. Although there is no agreement on the opportunity of using hematopoietic growth factors in advanced NSCLC, it could be interesting to evaluate escalation doses higher than 120 mg/m² with the support of granulocyte/colony-stimulating factor (G-CSF). We observed one PR at each dose level of epirubicin

ranging from 75 to 105 mg/m^2 and two PRs at 120 mg/m^2. These results would indicate the usefulness of a phase II study of epirubicin given at a dose of 120 mg/m^2 plus ifosfamide at 3 g/m^2 in advanced NSCLC.

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