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CLINICAL TRIAL REPORT

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Phase II study of intensive chemotherapy with carboplatin, ifosfamide and etoposide plus recombinant human granulocyte colony-stimulating factor and sequential radiotherapy in locally advanced, unresectable non-small-cell lung cancer

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Abstract From June 1991 to August 1994, 61 patients with stage III unresectable non-small-cell lung cancer (NSCLC; 16 cases of stage IIIA with N2 bulky disease and 45 cases of stage IIIB) were treated with ifosfamide given i.v. at 3 g/m^2 on day 1, carboplatin given i.v. at 200 mg/m^2 on days 1 and 2, etoposide given i.v. at 120 mg/m^2 on days 1–3 (ICE) and recombinant human granulocyte colony-stimulating factor (rhG-CSF) given s.c. at 5 μg/kg on days 4–13. Chemotherapy was given every 3 weeks for up to three cycles and, unless the disease progressed, was followed by thoracic radiotherapy on the tumor volume (total dose 60 Gy) and mediastinum (40 Gy). All patients had measurable or evaluable unresectable disease and a performance status (Eastern Cooperative Oncology Group) of 0–1. Only 61% of the enrolled patients received the full program of chemoradiotherapy according to the study design. At the end of sequential chemo-radiotherapeutic treatment, 41% of the patients had an objective response (24 partial responses and 1 complete response), 31% showed no change and 28% had progressive disease. The response rate noted for patients in stage IIIA with N2 bulky disease and that recorded for patients in stage IIIB did not differ significantly. The median time to progression was 5.4 months and the median survival was 8.2 months, with the 1-year survival rate being 31%. Sites of progression were mostly intrathoracic. Haematological toxicity was the main side effect, with grade III–IV thrombocytopenia being reported in 24% of the 165 courses of intensive ICE chemotherapy given. Febrile neutropenia was described in six courses (three patients). Non-haematological toxicities and radiotherapy-related side effects were generally mild and easily manageable. In conclusion, in unresectable stage III NSCLC a short program of moderately intensified ICE chemotherapy with rhG-CSF protection followed by sequential radiotherapy failed to increase the percentage of objective responses and reached a median survival comparable with that previously achieved with standard doses.

Key words NSCLC · Chemotherapy ·Radiotherapy · Colony-stimulating factors

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Introduction

At the time of clinical presentation, approximately 40% of patients with non-small-cell lung cancer (NSCLC) have locally advanced, unresectable disease (stages IIIA and B). For those tumours classified as stage IIIA with limited N2 lymph-node involvement the feasibility and activity of a short course of chemotherapy preceding surgery has been definitively proven, and randomized trials recently concluded in favour of the combined approach versus surgery alone [12, 13].

Patients with stage IIIB disease managed outside clinical trials usually receive definitive thoracic radiotherapy because it is commonly considered as standard therapy on the assumption that a small proportion of patients can be cured [4]. Unfortunately, the vast majority die as a result of the development of distant, extrathoracic metastases, and their median survival ranges between 8 to 10 months [5].

Relatively few data exist regarding the effectiveness of chemotherapy on the survival of patients with locally advanced, unresectable NSCLC, but in the majority of the cisplatin-based chemotherapy studies, higher response rates have been reported for stage III patients with a good performance status as compared with those in stage IV [2]. In recent years, two of five randomized trials in locally advanced NSCLC have demonstrated a small but definite improvement in long-term survival with combined chemo-radiotherapy [1, 7, 8, 10, 17]. In an attempt to improve further the antineoplastic efficacy of chemotherapy with minimal toxicity, a previous phase I/II study testing in unresectable NSCLC the combination of ifosfamide, carboplatin and etoposide achieved a 40% response rate along with a median survival of 8.6 months and a toxicity profiles that was surprisingly low [18].

The present phase II study was planned to investigate the efficacy and toxicity of ifosfamide, carboplatin and etoposide as intensive induction therapy followed by conventional high-dose thoracic radiotherapy in locally advanced (stage IIIA with N2 bulky disease and stage IIIB) NSCLC in patients with a good performance status. A secondary aim of the study was to evaluate the supporting role of recombinant human granulocyte colony-stimulating factor (rhG-CSF) in lessening haematological toxicity during induction chemotherapy.

Patients and methods

Patients enrolled in this study were previously untreated and had histologically or cytologically proven NSCLC clinically staged as either stage IIIA with N2 bulky disease or stage IIIB. N2 with bulky disease was defined as metastasis to the highest mediastinal lymph nodes, the paratracheal lymph nodes in the area of the thoracic inlet, with evidence of gross perinodal spread as documented by thoracic computerised tomography (CT) scan.

Eligibility criteria included an age of ≤ 70 years; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; measurable or evaluable disease; no prior chemotherapy, radiotherapy or surgery; weight loss of $\leq 5\%$ in the 6-month period preceding the diagnosis of NSCLC; no previous history of malignant disease (except for basal skin carcinoma or in situ cervical carcinoma); adequate renal (serum creatinine < 1.5-fold the upper value of the normal range), bone marrow (WBC count $> 3,500/mm^3$ and platelet count $> 150,000/mm^3$) and liver (bilirubin or SGOT < 1.2-fold the upper value of the normal range) function; no active cardiac, infective or metabolic disease; the absence of pleural effusion except in patients with a biopsy-proven negative histology; and the absence of superior vena cava syndrome.

Pretreatment evaluation included a complete physical examination, blood chemistry profile, chest X-rays, fiber bronchoscopy, thoracic CT scan, upper abdomen ultrasonography (or CT scan), and pulmonary function and blood-gas tests. Bone scintigrams and brain CT scans were performed only if clinically indicated.

Response and toxicity were evaluated according to WHO criteria [9] and the entrolled patients were evaluated according to an intent-to-treat policy. Response assessment was performed at the end of the chemotherapy program and then again at 1 month after the completion of radiotherapy. Patients were taken off study and followed for survival if they developed progressive disease or unacceptable toxicity or if they declined further therapy. Restaging procedures included a chest CT scan, upper abdomen ultrasonography or CT scan, and fiber bronchoscopy (only for complete responders). After the completion of radiotherapy, patients were followed every 6 weeks until death. Survival was calculated from the 1st day of chemotherapy until death or loss to follow-up.

Chemotherapy regimen

All eligible patients received carboplatin given i.v. at 200 mg/m^2 on days 1 and 2, ifosfamide given i.v. at 3,000 mg/m^2 on day 1, mesna given i.v. at 3,000 mg/m^2 on day 1 and etoposide given i.v. at 120 mg/m^2 on days 1–3. From day 4 to day 13, patients received rhG-CSF given s.c. at 5 μg/kg daily. Chemotherapy was repeated every 3 weeks for up to three courses. Patients were retreated if their WBC was $> 3,000/mm^3$ and their platelet count was $> 100,000/mm^3$. If not, treatment was delayed for 1 week and then, in the case of persistently low haematological values, the ifosfamide, carboplatin and etoposide doses were reduced by 25% for the subsequent courses. In the case of clinically documented infection or thrombocytopenia of $< 20,000/mm^3$ during the previous course of chemotherapy, a 25% dose reduction in the subsequent courses was required.

Thoracic radiotherapy

For radiotherapeutic treatment, high-megavoltage equipment and a thoracic CT scan simulator were required. Starting at 1 month after the completion of chemotherapy, a total dose of 60 Gy on the tumour volume and 40 Gy on the mediastinum was given 5 days per week at a daily dose of 2 Gy.

The primary tumour was encompassed by a minimal margin of 2 cm of normal tissue. The entire mediastinum was included from the suprasternal notch to at least 5 cm below the carina; tumours in the lower lobes required mediastinal irradiation to the diaphragm. Both hilar zones were encompassed in the treatment field, and the supraclavicular fossae were included in the radiation field only if clinically involved. The initial tumour volume was irradiated to a total dose of 40 Gy with an antero-posterior opposed field. Treatment was continued using a multiportal technique with reduced fields that included all of the originally detectable tumour. The

maximal dose allowed was 20 Gy to the controlateral lung, 45 Gy to the heart and 60 Gy to the esophagus.

Results

From June 1991 to August 1994, 61 eligible patients were entered from 5 cooperating centers. The patients' characteristics are listed in Table 1. There were significantly more patients in stage IIIB ($n = 45$) as compared with stage IIIA with N2 bulky disease ($n = 16$). Most of the enrolled patients had no weight loss in the 6-month period preceding the diagnosis of NSCLC and an ECOG performance status of 0. The median time from the diagnosis of NSCLC to the start of chemotherapy was 15 days (range 1–62 days).

Two patients died at home after 8 and 11 days from the beginning of the first course of chemotherapy, respectively, and were considered to have had progressive disease. In one case the cause of death was the onset of rapidly progressive pulmonary oedema, and in the other the cause of death remained unknown. No patient was lost to follow-up, and all patients were evaluable for survival estimation.

Dose reductions or treatment delays were required in only six patients, and three patients were removed from the study after two courses of chemotherapy because of persistent fever and neutropenia despite rhG-CSF administration and a 25% dose reduction in the second course of chemotherapy. Two and six patients stopped chemotherapy after one and two courses, respectively, due to clinically evident progression of the neoplastic disease, and four of these patients with loco-regional progression received thoracic radiotherapy immediately as salvage treatment.

Table 1 Patients' characteristics

Characteristic	Number of patients (%)
Patients enrolled	61
Patients evaluable for toxicity and response	59
M/F ratio	53/8
Median age (years)	57
Age range (years)	41–71
Histology:	
Squamous-cell carcinoma	26 (43)
Adenocarcinoma	18 (29.5)
Undifferentiated large-cell carcinoma	31 (21)
Undifferentiated NSCLC	4 (6.5)
Clinical staging:	
Stage IIIA	16 (26)
Stage IIIB	45 (74)
Weight loss:	
No	42 (67)
Yes (< 5%)	19 (33)
Performance status (ECOG):	
0	37 (61)
1	24 (39)

In all, 48 of 61 patients (79%) received the planned courses of chemotherapy, but only 37 were sequentially treated with thoracic radiotherapy (61%, 9 in stage IIIA and 28 in stage IIIB). Reasons for ineligibility for thoracic radiotherapy included distant metastasis (2 cases) and loco-regional progression documented at the end of chemotherapy (2 cases of pericardial effusion, 2 cases of pleural effusion, 3 cases of extensive parenchymal involvement), and in 2 cases of partial response the patients were immediately subjected to surgery.

At the end of sequential chemo-radiotherapeutic treatment, 25 objective responses [41%; 95% confidence interval (CI) 24–53%) were documented (1 complete response and 24 partial responses), in 19 patients (31%) the neoplastic disease progressed and in 17 (28%) it remained unchanged. The response rate was 42% for patients in stage IIIB (19/45; 95% CI 28–56%) and 37.5% for those in stage IIIA with N2 bulky disease (6/16; 95% CI 14–61%). Response according to histology was more frequently observed in squamous-cell carcinoma (13/25, 52%) than in adenocarcinoma (7/19, 37%) or large-cell carcinoma (3/13, 23%), but the difference was not statistically significant. The best response to chemo-radiotherapeutic treatment was documented in 18 cases after 2–3 courses of chemotherapy (72% of responding patients) and in 7 cases (28%) after thoracic radiotherapy, also including the case of complete response.

Five patients (two clinically staged as IIIB and three staged as IIIA with N2 bulky disease) were subjected to thoracotomy, in two cases after chemotherapy alone and in three cases after radiotherapy (total dose 36 Gy); four patients were radically resected (three pneumonectomies and one lobectomy), and in one patient the resection was considered incomplete. All the patients treated with surgery received adjuvant radiotherapy to reach to total dose of 60 Gy. At the time of this analysis, all five surgically treated patients are alive, two without evidence of recurrence of the neoplastic disease and the other three with distant metastasis (two cases) or loco-regional progression (one case).

The median time to progression for responsive and stable-disease patients was 5.4 months. The median follow-up is currently 12 months and the median survival is 8.2 months; the median survival is 9.7 months in responding patients, 7 months in stable disease and 4.6 months in progressive disease. The rate of local control at 1 year is 45%, and the 1- and 2-year rates of survival are 31% (15/48) and 0(0/8), respectively. In all, 12 of 15 patients surviving for more than 1 year from the diagnosis completed the full program of chemo-radiotherapy.

Sites of progression were intrathoracic in 34 patients (58%) and extrathoracic in 16 (26%); 89% and 81% of patients with squamous-cell carcinoma and undifferentiated large-cell carcinoma, respectively, progressed in the chest, whereas 42% of patients with adenocarcinoma had distant metastasis.

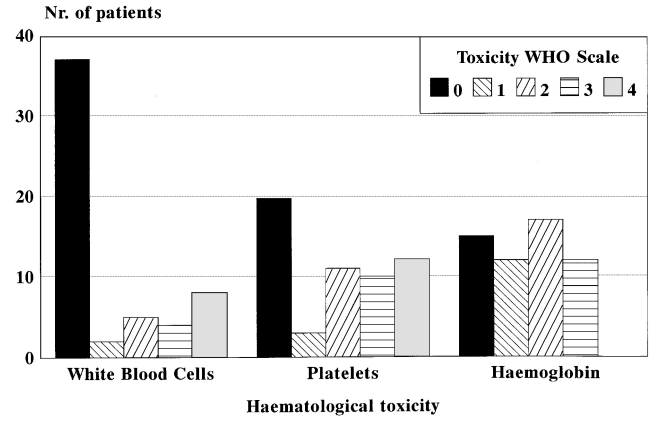

Fig. 1 Higher levels of haematological toxicity recorded for our patients during ICE induction chemotherapy

In 165 courses of intensive ICE chemotherapy with rhG-CSF support, grades 3 and 4 neutropenia and thrombocytopenia occurred in 20 (12%) and 40 (24%) courses, respectively (see Fig. 1). In six courses (three patients), grade IV neutropenia was febrile, and antibiotic treatment with cephalosporins (or acilureidopenicillins) and aminoglycosides was always promptly started and continued until the neutrophil count was > 500/ml. No septic episode was reported. Overall, 13 patients received red blood cell transfusions (total number of units given = 20), mainly through the 2nd and 3rd courses of chemotherapy, due to the clinical appearance of a haemoglobin fall under 8 gr/100 ml; in 6 patients, thrombocytopenia was managed with platelet transfusions.

No severe non-haematological complication was documented; grade 3 alopecia was reported in 20 patients, whereas episodes of chemotherapy-related nausea and vomiting, mainly prophylactically treated with serotonin-receptor antagonists, were absent (44 patients), mild (10 patients), or moderate (5 patients). Chemotherapy-related neuropathy and nephropathy were never reported. Radiotherapy-related side effects were mainly represented by mild to moderate oesophagitis during the 2nd to 3rd week of treatment, which was usually managed with H2 antagonists, and, rarely, by nausea and vomiting. No radiation pneumonitis was observed.

Discussion

The rationale for combining chemotherapy with radiotherapy in locally advanced NSCLC is based on the poor outcomes achieved with standard radiotherapy alone and the high frequency of distant metastases. The aim of combined chemo-radiotherapy is to improve both local control of the primary tumour and to decrease the incidence of distant metastasis with acceptable toxicity. Although the use of combined chemo-radiotherapy has produced a statistically significant survival gain in those trials employing cisplatin-containing chemotherapy, the overall impact on survival improvement can be considered modest at best. Improved control of both local and distant disease remains a formidable challenge [5].

As shown in a dose-finding study, the activity of the ICE regimen compares favourably with that of other regimens usually available for the treatment of patients with advanced unresectable NSCLC [18], and the results are especially encouraging when one considers that further dose escalation may be feasible with the prophylactic administration of colony-stimulating factors. Previously, several phase II studies in locally advanced and metastatic NSCLC tested ifosfamide and etoposide combined with cisplatin and reported objective responses in the range of 26–40% ([3, 15]; for additional references see Perez and Gandara [11]). In 11 patients with advanced NSCLC treated with a very dose-intensive ICE regimen with GM-CSF support, an excellent 64% response rate has been documented [6], whereas several other non-randomized phase II studies have demonstrated that with the use of colony-stimulating factors the interval between cycles may be reduced from 28 to 21 days and even to 14 days or, alternatively, dose increases can be undertaken, but neither trial suggested a higher response rate or survival gain [14].

In our study, objective responses were equally observed in patients in stage IIIA with N2 bulky disease and in patients in stage IIIB; the result could be considered satisfactory for the latter group, whereas additional information is needed on the stage IIIA patients, but in any case the intensification of chemotherapy failed to improve the percentage of responses. In comparison with the higher-dose schedule tested in the pilot study by van Zandwijk et al. [18], in the present study the intended dose intensity for ifosfamide was comparable, whereas those for carboplatin and etoposide were increased 1.5- and 1.6-fold, respectively. Nevertheless, the response rate was nearly the same in both studies. In contrast, the comparative analysis for dose intensity of our study with that of Krigel et al. [6] showed the same intended dose intensity for carboplatin, whereas those for ifosfamide and etoposide were 1.4- and 2.5-fold higher, respectively, in the latter study. This finding emphasizes again that in clinical practice, more is not necessarily better and the existence of a dose-response curve, at least for dose increases on the order of those usually tested for most of the currently used chemotherapeutic agents, remains to be demonstrated.

In squamous-cell carcinoma and undifferentiated large-cell carcinoma, most of the patients relapsed in the thorax; therefore, an optimization of the local treatment is needed, mainly through altered-fractionation radiotherapeutic schedules (accelerated fractionation,

hyperfractionation and accelerated hyperfractionation), which have been shown to decrease the repopulation of tumor cells and to ameliorate the sparing of late-reacting normal tissues [4, 5].

Thrombocytopenia was the most common side effect, followed by asymptomatic grades 3 and 4 neutropenia, and in three cases, in spite of prophylactic rhG-CSF administration, febrile neutropenia was documented. However, neither life-threatening bleeding episodes nor infectious complications were reported.

The tendency toward cumulative toxicity, as shown by increasing requirements for red blood cell transfusions during the second and third cycles, and the lack of a protective effect of currently available colony-stimulating factors on platelet formation indicate that only slight increases in the doses of ifosfamide, carboplatin and etoposide could be further allowed. In the next few years, newer cytokines [interleakin 3 (IL-3), PIXY321, IL-6, stem-cell growth factor] will be introduced into clinical practice. These molecules generally act at an earlier time point in the haematopoietic cascade, and some of them have shown activity on megakaryocyte progenitors. In a recent trial testing rhG-CSF alone versus sequential or simultaneous administration of IL-3 and rhG-CSF after ICE chemotherapy, the greatest degree of protection seemed to be achieved with IL-3 and rhG-CSF given simultaneously [16].

In conclusion, the present study showed the feasibility of moderately intensive ICE induction chemotherapy in NSCLC patients in stage IIIA with N2 bulky disease and patients in stage IIIB, but the overall results obtained in terms of response rate, local control and median survival seem to overlap considerably with those achieved with a standard sequential chemoradiotherapeutic approach. In spite of the apparently modest results reported for the present study, further randomized trials will be necessary, especially in stage IIIB NSCLC, to determine the true contribution of this approach as compared with an established cisplatin-based regimen followed by sequential radiotherapy.

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