CARBOPLATIN IN ASSOCIATION WITH ETOPOSIDE AND EITHER ADRIAMYCIN OR EPIRUBICIN FOR UNTREATED SMALL CELL LUNG CANCER: A DOSE ESCALATION STUDY OF CARBOPLATIN

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A multi-center, open trial was conducted to determine the maximal tolerable dose of carboplatin in combination with conventional doses of both etoposide and an anthracycline for the treatment of previously untreated small cell lung cancer (SCLC) patients. Ninety-five patients [48 with limited disease (LD) and 47 with extensive disease (ED)] received a total of 376 courses of treatment. Carboplatin was given on day 1 at a dose of 250 mg m$^{-2}$ in 60 courses, 300 mg m$^{-2}$ in 69, 330 mg m$^{-2}$ in 236 and 350 mg m$^{-2}$ in 11, with 120 mg m$^{-2}$ etoposide on days 1, 3 and 5 and either 40 mg m$^{-2}$ adriamycin or 60 mg m$^{-2}$ epirubicin on day 1. Epirubicin was not administered before carboplatin reached the dose of 330 mg m$^{-2}$. Courses were repeated every 3 weeks. The main toxicity was hematological. The first course of therapy induced a dose-dependent decrease of leucocyte, neutrophil and platelet counts: all patients, except one, who received 350 mg m$^{-2}$ carboplatin had a neutropenia below 200 $\mu l^{-1}$ and a thrombopenia below 100,000 $\mu l^{-1}$. Three patients died of septicemia. Other toxicities were well tolerated. After three courses, patients were re-staged by performing a mandatory fiberoptic bronchoscopy and a thoracic computed axial tomography (CAT). The overall objective response rate for 86 evaluable patients was 91% (98% for LD) with 21% complete remissions (30% for LD). All 23 hepatic and six brain sites, evaluable after chemotherapy alone, responded. This new combination, in which the recommended dose of carboplatin is 330 mg m$^{-2}$, should be evaluated in a prospective study for SCLC.

Key words: Small cell lung cancer, Carboplatin, Dose escalation.

INTRODUCTION

Carboplatin is a second generation platinum coordination complex that, in phase II studies, has demonstrated high activity in SCLC.\textsuperscript{1,2} It has been shown to be less emetogenic and to produce less nephrotoxicity, neurotoxicity or ototoxicity than cisplatin, but more myelotoxicity.\textsuperscript{3-5} Etoposide has a well known effect on SCLC\textsuperscript{6} and is now widely used in combination with other drugs for induction treatment.\textsuperscript{7} Smith \textit{et al.}\textsuperscript{8} reported an 85% objective response rate using a combination of carboplatin with etoposide, but were disappointed by the short median response duration and survival time. Anthracyclines are also active drugs in the therapy of previously untreated SCLC. Adriamycin achieves a 30% objective response rate\textsuperscript{9} and epirubicin has recently been shown to have similar activity.\textsuperscript{10} However, compared to adriamycin, the epirubicin cardiac toxicity is reduced.\textsuperscript{11}

In previous studies, the maximum tolerated dose of carboplatin given alone was 400 mg m$^{-2}$.\textsuperscript{3,4,8} In one study, a dose of 300 mg m$^{-2}$ was given in association with etoposide.\textsuperscript{8} The objective of our study was two-fold: (1) to determine the recommended dose of carboplatin\textsuperscript{12} in previously untreated SCLC, when given in association with conventional doses of etoposide and either adriamycin or epirubicin, and...
(2) to evaluate the anti-tumor activity of these regimens.

PATIENTS AND METHODS

Patients

Ninety-five previously untreated patients with histologically and/or cytologically demonstrated SCLC entered into this study from December 1985 to July 1987. There were 80 men and 15 women with a median age of 60 yr (range 35–75). Forty-eight of these patients had LD and forty-seven ED. The Karnofsky index ranged from 30 to 100 with a median of 80. No patient had received chemotherapy prior to this treatment; however, two patients had been treated with radiotherapy for central nervous system (CNS) metastasis.

Staging investigations

Before treatment, all patients underwent physical examination, biological analysis (plasma urea and electrolytes, serum creatinine, SGOT, SGPT, LDH, complete blood counts, urine analysis), fiberoptic bronchoscopy with washing, brushing and biopsy, chest X-ray, radionuclide bone scan with subsequent bone X-ray of abnormal areas, bone marrow aspirate and biopsy, and CAT scan of the thorax, abdomen and brain.

Between courses, complete blood counts, plasma urea and serum creatinine were determined on a weekly basis by either the patient’s general practitioner or the hospital center.

Response to chemotherapy was analysed after the third course of therapy. Chest X-rays, thoracic CAT scans, fiberoptic bronchoscopies and investigations of any initially positive tests were repeated for all cases.

LD was defined as disease confined to one hemithorax, mediastinal, hilar and ipsilateral supraclavicular areas that could be encompassed with a single radiation treatment portal. Pleural effusion or extrathoracic spread beyond the limits previously stated was defined as ED.

Drug administration

Carboplatin was supplied by Bristol Benelux Laboratories and was administered in a 15 min infusion of 250 ml normal saline on day 1. It was given in 376 courses and administered at the planned dose of 250 mg m$^{-2}$ in 60 courses, at 300 mg m$^{-2}$ in 69, at 330 mg m$^{-2}$ in 236, and at 350 mg m$^{-2}$ in 11. Carboplatin dosage was increased upon agreement from all authors (meeting every 3 months) that the clinical toxicity at the usual dosage was tolerable. At this point, all of the subsequent cycles of therapy were given at the newly increased dose of carboplatin. Etoposide was administered at a dose of 120 mg m$^{-2}$ during a 15 min infusion in 250 ml normal saline on days 1, 3 and 5. Forty mg m$^{-2}$ adriamycin was given during a 15 min infusion in 250 ml 5% dextrose on day 1 for all the patients who received 250 and 300 mg m$^{-2}$ Carboplatin and for the first 19 patients who were included at 330 mg m$^{-2}$. Afterwards we switched from adriamycin to epirubicin (60 mg m$^{-2}$) for new patients admitted to the study, first at 330 mg m$^{-2}$ and then at 350 mg m$^{-2}$ carboplatin. Treatment was repeated every 3 weeks. In the presence of thrombopenia < $10^4$ µl$^{-1}$ or neutropenia < 2000 µl$^{-1}$, the following course was postponed one or more weeks until hematological recovery.

After three courses of chemotherapy, treatment was left at the discretion of the different investigators and depended on the patient’s characteristics (age, response, extension of disease), and the medical expertise. Eighteen patients in complete remission (CR) or partial remission (PR) entered a phase I study of either high dose chemotherapy (cyclophosphamide, BCNU, melphalan) with autologous bone marrow transplantation or the same drugs at conventional dosage; 22 LD patients (9 CR, 13 PR) received thoracic radiotherapy directed at the primary site. The other responding patients received further courses of induction therapy until the occurrence of unacceptable toxicity or tumor progression. Prophylactic cranial irradiation was not routinely administered in this study.

Response and toxicity

Tumor response was defined according to standard criteria. CR was defined as disappearance of all signs of SCLC for 30 days. PR was defined as the reduction by at least 50% in the product of the two greatest perpendicular diameters of all tumor masses for 30 days. Progressive disease (PD) was defined as the progression by at least 25% of a known localisation or as the appearance of a new SCLC lesion. Stable disease (SD) included patients without PD who did not qualify for PR. Toxicity was graded according to standard World Health Organisation (WHO) criteria.