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Phase II trial of carboplatin (JM8) in treatment of patients with malignant mesothelioma

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Summary. Seventeen patients with malignant mesothelioma were treated in a phase II study with carboplatin, a cisplatin analogue without significant nephrotoxicity or neurotoxicity. The drug was given in a dose of 300–400 mg/m^2 by i.v. infusion, repeating at 28-day intervals. One patient achieved a complete clinical and radiological remission of 15 months' duration, and a second patient achieved a partial response of 11 months' duration (overall response rate 12%; overall response rate in previously untreated patients 20%). Four other previously untreated patients achieved symptomatic relief. Treatment was well tolerated without severe side-effects. Carboplatin, like most other cytotoxic drugs, is active only in a small minority of patients with mesothelioma, but its ability to achieve occasional good reponses and frequent symptomatic relief, combined with low toxicity, may justify a short therapeutic trial in patients whose tumour is symptomatic.

Introduction

Carboplatin is a cisplatin analogue which does not cause significant nephrotoxicity or neurotoxicity and which is less emetic than the parent compound [7, 14]. It has established clinical activity against several tumour types; in particular it is as effective as cisplatin in ovarian carcinoma [16] and is very active in the treatment of small cell lung cancer [14]. In this phase II study we have investigated the efficacy of carboplatin in the treatment of malignant mesothelioma, a tumour for which conventional chemotherapy is usually ineffective [1, 15].

Patients and methods

In all 17 patients (14 men, 3 women) with histologically proven malignant mesothelioma were entered into the study; the median age of the group was 57 (range 22–78) years. The disease was pleural in 13 and peritoneal in 4. According to the modified staging schema of Butchart [3], 3 patients had stage I disease, 8 patients stage II, 4 patients stage III, and 2 patients stage IV.

Previous treatment. Three patients had failed previous chemotherapy, which included adriamycin, cyclophosphamide, ifosfamide, bleomycin and methotrexate. Four patients had radiotherapy to the chest. Ten patients were previously untreated.

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Dose and schedule. JM8 was formulated and supplied by Bristol-Myers International and by the NCI, Bethesda, Md. It was given at a dose of 400 mg/m^2 i.v. to ten patients and 300 mg/m^2 i.v. to seven patients (because of compromised bone marrow from previous treatment in 3 patients, age >70 in 2 patients and >25% reduction in ^{51}Cr-EDTA clearance in 2 patients). The drug was given in a 1-h infusion of 500 ml in 5% dextrose and was repeated at 28-day intervals. Patients were treated with prophylactic antiemetics (usually Lorazepam 2 mg i.v. and metaclopramide 20 mg i.v.) stat. and repeated 5 h after chemotherapy.

Patients were initially treated with 2 courses of JM8 unless there was progressive disease after the first course. In those who achieved symptomatic relief treatment was then continued until complete remission, stable partial remission or recurrence of symptoms. Two responding patients received 10 and 13 courses of treatment.

Staging investigations. Prior evaluation included a full clinical examination, full blood count, biochemical profile, chest X-ray, CT scan of chest or abdomen. The sum of the products of two perpendicular diameters were recorded for subcutaneous nodules. Renal function was further assessed by ^{51}Cr-EDTA clearance.

Patients were re-assessed with a full blood count at 3 weeks after each course of treatment at the time of anticipated peripheral blood count nadir [7], and initial investigations excluding CT scan were carried out before each course of therapy. Repeat CT scans were carried out after two courses in patients whose tumour appeared stable or was responding to treatment according to clinical and radiological examination.

Response and toxicity. Complete remission (CR) was defined as total disappearance of all tumour on repeat CT scan for at least 2 months, and partial remission (PR) as reduction of more than 50% in the product of measurable disease on repeat CT scan (taking the slice containing the largest cross section of tumour) or in subcutaneous nodules for a duration of at least 1 month. Toxicity was graded according to WHO criteria [17].

Results

One patient with stage I peritoneal mesothelioma achieved a CR of 15 months' duration and another with stage II pleural mesothelioma achieved a PR of 11 months' dura-

tion, giving an objective response rate of 12% (95% confidence limits 0–27%). Both responses were seen in previously untreated patients, and in this group the response rate was 20% (95% confidence limits 0–45%). Four other previously untreated patients achieved symptomatic relief lasting 1, 3+, 4 and 14 months.

The patient achieving a CR survived 17 months from the start of treatment, and the patient achieving a PR survived 26 months. One patient among the improved group is still alive 5 months from the start of treatment, while the rest died at 4, 7 and 28 months. All non-responders died within 6 months of starting treatment, except one who died at 15 months.

Toxicity

In general treatment was well tolerated. Five patients (29%) had transient nausea, and a further eight (47%) experienced vomiting, but this was mild and transient (WHO grade II) in all but one patient. Only one patient had an episode of leucopenia (WHO grade III), and one patient had mild (WHO grade I) thrombocytopenia. No other toxicity was seen.

Discussion

The incidence of mesothelioma is rising [11], and treatment remains unsatisfactory. Surgery is not effective except perhaps in a small proportion of early-stage patients [2, 6]. Radiotherapy may palliate pain in some patients, but there is no consistent evidence for a survival benefit [5, 9].

Chemotherapy has likewise proved disappointing. Of the cytotoxic agents which have been assessed, there is evidence to suggest that the anthracyclines are the most active. In a small pooled series of 36 patients treated with doxorubicin, an overall response rate of 44% was reported [1], and a new daunorubicin analogue, detorubicin, achieved a 43% response rate including 10% complete remission in 21 patients with measurable disease [8]. In contrast, a randomised trial comparing doxorubicin with cyclophosphamide revealed no responders to either drug [15]. Response rates of up to 40% in previously untreated patients have been reported with doxorubicin-containing regimens, without clear-cut evidence of survival benefit and with considerable toxicity, but in uncontrolled studies [4]. Cisplatin, the parent compound of carboplatin, appears to have little efficacy, with an objective response rate of 10% at moderate dosage [1] and 11% at high dosage (120 mg/m^2) [10]. Results with intracavitary cisplatin are harder to assess; the same authors report 2/11 responders in one paper [12] and 4/8 in another [13].

This study has demonstrated that carboplatin also has low activity against mesothelioma, and it might be concluded that the drug has no role in the management of this disease. However, the two responses which were achieved were impressive both in duration and in clinical benefit. Good symptomatic relief was also obtained in four other patients, and in general the drug was well tolerated. On this basis there may be a case for a short therapeutic trial of carboplatin in patients with symptomatic mesothelioma, reserving more prolonged teatment for those few who achieve initial clinical benefit.

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References

1. Aisner J, Wiernik PH (1981) Chemotherapy in the treatment of malignant mesothelioma. Semin Oncol 8: 335–343
2. Antman KH (1980) Current concepts: Malignant mesothelioma. N Engl J Med 303: 200–202
3. Antman KH (1981) Clinical presentation and natural history of benign and malignant mesothelioma. Semin Oncol 8: 313–320
4. Antman KH, Blum RH, Greenberger JS, Flowerdew G, Skarin AT, Canellos GP (1980) Multimodality therapy for mesothelioma based on a study of natural history. Am J Med 68: 356–362
5. Brady LW (1981) Mesothelioma – the role of radiation therapy. Semin Oncol 8: 329–334
6. Butchart EG, Ashcroft T, Barnsley WC, Holden MP (1981) The role of surgery in diffuse malignant mesothelioma of the pleura. Semin Oncol 8: 321–328
7. Calvert AH, Harland SJ, Newell DR, Siddik ZH, Jones AC, McElwain TJM, Raju S, Wiltshaw E, Smith IE, Baker JM, Peckham MJ, Harrap KR (1982) Early clinical studies with cis-diammine I, I-cyclobutane dicarboxylate platinum II. Cancer Chemother Pharmacol 9: 140–147
8. Colbert N, Vannetzel JM, Izrael V, Schlienger M, Milleron B, Blanchon F, Herman D, Akoun G, Roland J, Chatelet F, Laugier A (1985) A prospective study of detorubicin in malignant mesothelioma. Cancer 56: 2170–2174
9. Gordon W, Antman K, Greenberger JS, Weichselbaum RR, Chaffey JT (1982) Radiation therapy in the management of patients with mesothelioma. Int J Radiat Oncol Biol Phys 8: 19–25
10. Mintzer D, Kelsen D, Frimmer D, Heelan R, Gralla R, Ochoa M (1984) Phase II trial of high-dose cisplatin in patients with malignant mesothelioma. Proc Am Soc Clin Oncol 25: 258
11. Newhouse M (1981) Epidemiology of asbestos-related tumours. Semin Oncol 8: 250–257
12. Pfeifle CE, Howell SB, Markman M (1984) Intracavitary cisplatin for mesothelioma. Proc Am Soc Clin Oncol 25: 258
13. Pfeifle CE, Howell SB, Markman M (1985) Intracavitary cisplatin chemotherapy for mesothelioma. Cancer Treat Rep 69: 205–207
14. Smith IE, Harland SJ, Robinson BA, Evans BD, Goodhart LC, Calvert AH, Yarnold JR, Glees JP, Baker J, Ford HT (1985) Carboplatin: A very active new cisplatin analogue in the treatment of small cell lung cancer. Cancer Treat Rep 69: 43–46
15. Sorensen PG, Bach F, Bork Ellen, Hansen HH (1985) Randomised trial of doxorubicin versus cyclophosphamide in diffuse malignant pleural mesothelioma. Cancer Treat Rep 69: 1431–1432
16. Wiltshaw E, Evans BD, Jones AC, Baker JM, Calvert AH (1983) JM8, successor to cisplatin in advanced ovarian carcinoma? Lancet 1: 587
17. World Health Organisation (1979) WHO handbook for reporting the results of cancer treatment. WHO, Geneva (Offset publication no 48)

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