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Carboplatin in malignant mesothelioma: A phase II study of the Cancer and Leukemia Group B

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Summary. Carboplatin (400 mg/m^2) was given at 28-day intervals to 41 patients with malignant mesothelioma. In all, 40 patients were eligible and evaluable for response. Partial responses were seen in 2 cases (5%); regression of evaluable disease, in 1 patient (2%); and stable disease, in 19 subjects (48%). A median of two doses of carboplatin per patient resulted in mild toxicity. Leukopenia ($\leq$2,000 cells/μl) and thrombocytopenia (<100,000 cells/μl) were seen in only 6% and 20% of the patients, respectively. Median survival from study entry was estimated at 7.1 months, with a 1-year survival of 25% ±7%. Carboplatin given at a dose of 400 mg/m^2 at 28-day intervals shows minor activity against malignant mesothelioma.

Introduction

Malignant mesothelioma continues to be difficult to treat with chemotherapy. Although agents such as doxorubicin [1, 4], high-dose cisplatin [16], mitomycin C [6], and, possibly, high-dose methotrexate [11] show marginal activity against this disease, an urgent need exists to find new treatment modalities [2]. Thus, in 1984 the Cancer and Leukemia Group B (CALGB) began prospective evaluations of new agents or combinations in this disease [10]. Since carboplatin showed some activity as a single agent in a nude mouse model of mesothelioma [9] and in two smaller phase II trials [8, 15], we initiated this phase II trial.

Patients and methods

Patients with histologically documented malignant mesothelioma who had measurable or evaluable disease were eligible for the study. They were also required to have the following: (a) a CALGB performance score of 0–2, (b) adequate nutrition, (c) an age of >15 years, (d) no prior malignancy, (e) no serious underlying medical illness, (f) a life expectancy of >2 months, and (g) no prior cytotoxic chemotherapy. An interval of >4 weeks since the completion of previous radiotherapy was required before the start of carboplatin treatment. Subjects could not have had surgery within 2 weeks of starting carboplatin. All patients gave written informed consent. The patients were required to have a granulocyte count of >1,800/μl, a platelet count of >100,000/μl, a hemoglobin level of >10 gm/dl, a serum bilirubin value of <1.5 × the upper limit of normal, a serum creatinine level of <1.8 mg/dl, and creatinine clearance of $\geq$60 ml/min.

This study was performed using a two-stage phase II design. When 20 patients had been entered in the study, accrual was suspended until at least one response had been confirmed [5]. After one response was documented, the study reopened for final accrual. Central pathology review by two reviewers (J.M.C., Y.S.) of the CALGB pathology committee was required for all patients. In all, 90% of cases required a thoracotomy for diagnosis, whereas 10% underwent a needle biopsy suitable for diagnosis. Thus far, these two reviewers have reviewed slides on 29 and 28 patients, respectively.

The results of the pathology review are shown in Table 1. Virtually all of the patients were retrospectively classified as having definite, probable, or possible mesothelioma. Only one case was classified by both reviewers as not having mesothelioma; that tumor (CALGB patient 40045) was reviewed as a malignant schwannoma and the patient was excluded from the analysis. Another subject, classified as "other" by one reviewer and as "probable" by the other, had a presentation, a clinical course, and radiographic findings that were typical of mesothelioma and was therefore included in the analysis.

As part of the data quality-assurance program of CALGB, members of the Data Audit Committee make site visits to all institutions at least once every 3 years. Audit Committee members verify compliance with Federal regulations and protocol requirements, including eligibility, treatment, tumor response, and follow-up in a sample of protocols at each institution. The medical records of a cohort of 11 (27%) patients entered in this study were subjected to such on-site review.

Treatment. Carboplatin was to be given at a dose of 400 mg/m^2 as a 30-min infusion every 28 days for a minimum of 2 courses unless rapid disease progression was documented. This dose was to be reduced by 25% if the platelet count on the day of treatment was 75–100,000/μl or the total granulocyte count was 1,200–1,799/μl. Treatment was to be discontinued for a platelet count of <75,000/μl and a granulocyte count of <1,200/μl. Dose reductions of 50% were required when the serum creatinine value was between 1.5 and 2 mg/dl on the day of treatment, and treatment was discontinued when the serum creatinine level was >2 mg/dl. Dose escalation was not permitted. Standard CALGB response

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Table 1. Pathology review by two pathologists of CALGB study 8638: carboplatin in mesothelioma

	Reviewer 1 (Y.S.)	Reviewer 2 (J.C.)
Diagnosis:		
Definite mesothelioma	19 (66%)	15 (54%)
Probable mesothelioma	6 (21%)	7 (25%)
Possible mesothelioma	3 (10%)	3 (11%)
Other	1 (3%)	2 (7%)
Not done		1 (4%)
Histologic subtype:		
Epithelial	18 (62%)	20 (71%)
Mixed	4 (14%)	0 (0)
Sarcomatoid	5 (17%)	4 (14%)
Not done	2 (7%)	4 (14%)
Special studies:		
Mucicarmine:		
Negative	16 (55%)	14 (50%)
Positive	10 (34%)	1 (4%)
Not done	3 (10%)	10 (36%)
Unknown	0 (0)	3 (11%)
PAS-diastase-resistant:		
Negative	19 (66%)	17 (61%)
Positive	1 (3%)	2 (7%)
Not done	6 (21%)	6 (21%)
Unknown	3 (10%)	3 (11%)
Hyaluronidase-alcian blue[a]:		
Negative	2 (7%)	2 (7%)
Positive	1 (3%)	0 (0)
Indeterminate	1 (3%)	1 (4%)
Not done	19 (66%)	22 (79%)
Unknown	6 (21%)	3 (11%)
Immunohistochemistry:		
Keratin proteins:		
Strong	15 (52%)	14 (50%)
Moderate	5 (17%)	6 (21%)
Weak	1 (3%)	0 (0)
Absent	1 (3%)	1 (4%)
Not done	7 (24%)	7 (25%)
CEA:		
Weak	0 (0)	1 (4%)
Absent	21 (72%)	20 (71%)
Not done	8 (28%)	7 (25%)
Mesothelial localization pattern:		
No	2 (7%)	0 (0)
Yes	16 (55%)	15 (54%)
Indeterminate	4 (14%)	4 (14%)
Unknown	7 (24%)	9 (32%)

[a] Positive denotes hyaluronidase-resistant alcian blue-positive material found in secretory granules of tumor cells or in the lumen of tubules formed by the tumor

criteria were used. Response was assessed at 2-month intervals by chest radiographs and computerized axial tomographic (CAT) scans.

Results

In all, 41 patients were treated between February 1987 and February 1988 at 17 different CALGB institutions, and study records are available on all 41 subjects. As 1 patient was ineligible due to pathology review and was excluded from further analysis, 40 subjects were evaluable for response. Patient characteristics are shown in Table 2. A total of 197 cycles of carboplatin were given (median, 2; mean, 4; range, 1–26+). There were 2 partial responses and 1 regression of evaluable disease, for an overall response rate of 7% (95% confidence interval, 2%–21%); these 3 responders received a median of 8 doses of carboplatin (range, 4–13). A total of 19 patients were declared to have "stable" disease (defined as a of <50% decrease or an increase of no more than 25% in tumor size for at least 8 weeks); these subjects received a median of 5 (range, 2–26+) doses of carboplatin. In all, 18 patients had progressive disease; they received a median of 2 (range, 1–6) doses of carboplatin. Only three patients received one dose of carboplatin before being classified as having progressive disease; upon review, the performance status of two of these subjects was probably worse than 2, and the third patient refused a second dose. Thus, virtually all patients received an adequate therapeutic trial.

Table 2. Patient characteristics in carboplatin-treated malignant mesothelioma

Characteristics	Patients (*n*)	Percentage
Sex: M	32	80%
F	8	20%
Age: <60 years	16	40%
>60 years (median, 62 years; range, 41–75 years)	24	60%
Performance status:		
0 = normal	15	38%
1 = ambulatory	19	48%
2 = <50% in bed	6	15%
Primary site:		
Pleural	34	90%
Nonpleural	6	10%
Asbestos exposure[a]:		
Yes	20	50%
No	15	38%
Unknown	5	12%
Prior radiotherapy	4	10%

[a] Asbestos exposure as reported by the treating physician

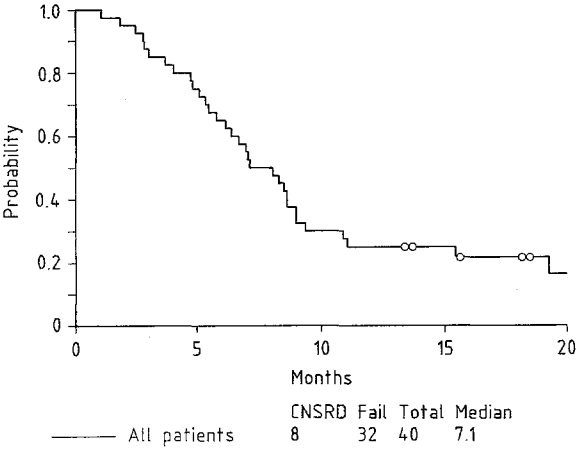

Fig. 1. Survival of patients with malignant mesothelioma after treatment with carboplatin

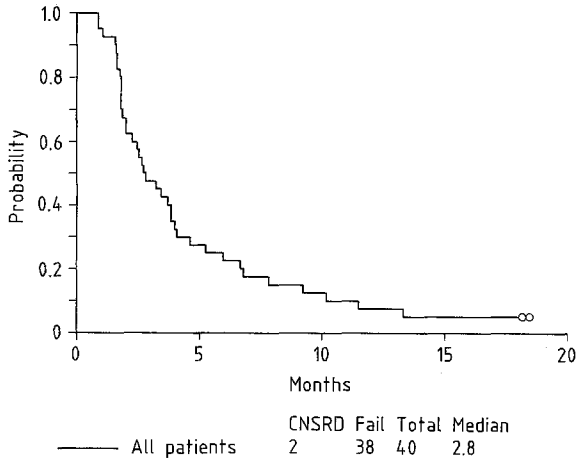

Fig. 2. Failure-free survival of patients with malignant mesothelioma after treatment with carboplatin

Table 3. Toxicity of carboplatin in a CALGB phase II study

Toxicity	Percentage of patients
Leukopenia, <2,000/μl (WHO grades 3 and 4)	6%
Hemoglobin, 7.5–8.5 gm/100 ml (WHO grade 3)	25%
Thrombocytopenia, <100,000/μl (WHO grades 3–4)	20%
Severe nausea and vomiting	28%

The median survival was 7.1 months, with an estimated 1-year survival of 25%±7% (Fig. 1). The median failure-free survival was 2.8 months (Fig. 2). Patients who had measurable disease or had not been exposed to asbestos had a longer time to treatment failure ($P = 0.009$ and $P = 0.01$, respectively) but experienced no significant prolongation of survival.

Toxicity

The maximal toxicities experienced by the 40 patients are shown in Table 3. The median nadir WBC was 4,500/μl (range, 900–11,800/μl) and only one patient experienced neutropenic fever. The median nadir platelet count was 184,000/μl (range, 9–540/μl) and only one patient requried platelet transfusions. Grade 3 nausea (no significant oral intake) or vomiting (6–10 episodes within 24 h) occurred in 28% of patients. Aside from bone-marrow suppression and nausea and vomiting, there were essentially no severe or life-threatening toxicities. In all, 3% patients experienced severe diarrhea, peripheral neuropathy, or fatigue. There were no toxic deaths. The median initial serum creatinine level was 0.9 mg/100 ml, and the median off-study serum creatinine value was the same.

Discussion

This large phase II trial demonstrated that carboplatin shows minor activity (response rate, 7%, 95% confidence interval, 2%–21%) against malignant mesothelioma. Although 48% of patients had stable disease, this was most likely the result of both the slowly progressive nature of this malignancy in some of these patients and the current limitations of imaging techniques in quantifying modest tumor enlargement (or regression).

Given the modest myelosuppression (and response rate) experienced by patients on study, carboplatin dose escalation seems feasible. In patients who had received no prior chemotherapy and minimal prior radiotherapy, this study suggests that the starting dose could be escalated. The appropriate dose-escalation scheme is unknown but should be based on renal function, not body-surface area [7, 12]. The toxicities of higher-dose carboplatin could be formidable in this population [13, 19]. Whether dose escalation could increase this response rate is unknown.

The role of carboplatin in the therapy of mesothelioma is unclear. Raghavan et al. [18] reported 1 complete remission and 4 partial remissions in 31 patients treated with carboplatin at a dose of 150 mg/m^2 daily $\times 3$. Cantwell et al. [8] reported responses in 2 of 9 cases, whereas Mbidde et al. [15] reported 2 responses in 17 treated patients. These three phase II studies plus the current report on carboplatin in mesothelioma yield an overall regression rate of 12% (12/97). This compares favorably with single-agent activity summarized for doxorubicin (18%), cisplatin (10%) and cyclophosphamide (28%) [4].

This study population was similar to those of most mesothelioma series in the literature in that there was a predominance of men over women (80% vs 20%), a considerable history of asbestos exposure, and a high frequency of pleural primaries [2, 3, 20, 21]. These therapeutic findings are thus easily generalized to other patients. The CALGB performed this phase II study within 1 year. Given the pressing need to identify active agents, cooperative oncology groups should consider combining phase II studies in mesothelioma with concurrent scientific companion studies to obtain a better understanding of the basic biology of mesothelioma [14, 17].

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