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Short report

High-dose paclitaxel plus G-CSF for malignant mesothelioma: CALGB phase II study 9234

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Summary

Background: New agents with activity in mesothelioma are sorely needed. The Cancer and Leukemia Group B (CALGB) therefore performed a phase II study of high-dose paclitaxel in patients with malignant mesothelioma who had no prior chemotherapy.

Patients and methods: Thirty-five patients accrued to this multi-institutional phase II study of paclitaxel given as a 24-hour infusion at 250 mg/m^2 every three weeks plus filgrastim (G-CSF) 300 mcg subcutaneously days 3–18.

Results: There were three (9%) regressions of evaluable disease. The median survival was five months (95% confidence interval (95% CI): 1.9–9.6 months), the one-year survival rate was 14% and the two-year survival rate was 6%. Toxicity was tolerable with one death from pneumonia (without neutropenia) on day 18 and a 23% rate of grade 4 granulocytopenia.

Conclusions: The level of activity seen with paclitaxel is similar to that seen in other CALGB trials of the single agents carboplatin, trimetrexate and 5-azacytidine. Future studies of of paclitaxel (at lower doses) in combination with synergistic agents could be considered.

Key words: mesothelioma, paclitaxel

Introduction

The chemotherapy of mesothelioma has been recently reviewed [1]. Although some agents appear to have modest activity (doxorubicin, mitomycin, edatrexate, dihydroazacytidine, cisplatin and carboplatin), response duration is usually less than four months. No trials have compared the survivals of patients treated with chemotherapy to untreated patients. Although Solheim et al. reported a 37% response rate to high-dose methotrexate in a series of 60 patients with a median survival of 11 months [2], there have been no well-powered confirmatory trials of that report. In light of the poor track record of chemotherapy, the CALGB has been investigating single agents or combinations in sequential phase II studies to determine if an effective chemotherapeutic drug or regimen can be found [3–9]. Given the wide range of activity of the taxanes in multiple tumor types, the CALGB initiated this phase II study of high-dose paclitaxel in the treatment of chemotherapy-naïve patients with malignant mesothelioma.

Study design

Patients with histologically confirmed malignant mesothelioma (epithelial, sarcomatoid, or mixed in cell type) who had received no prior chemotherapy were accrued to this study. Standard CALGB eligibility criteria were used [3–7].

The paclitaxel dose was 250 mg/m^2 infused via a central line over 24 hours every three weeks. No dose escalation was permitted. Dose modifications for hematologic, cardiovascular and neurologic toxicities were defined. Filgrastim (G-CSF) was given at a dose of 300 mcg subcutaneously on days 3 to 18 of each cycle but was to be stopped when a white count of $\geqslant$ 100,000/μl was achieved. Treatment continued until tumor progression, death, or unacceptable toxicity developed.

Response criteria

The CALGB response criteria for mesothelioma chemotherapy trials are unchanged since 1990 [3–7], and are used in this trial.

Statistical methods

Eighteen patients were to be entered into the first stage of the study. If at least three of these 18 patients showed evidence of response, then an additional 17 patients were to be entered onto the study for a total of 35. If fewer than three of the first 18 patients responded, the trial was

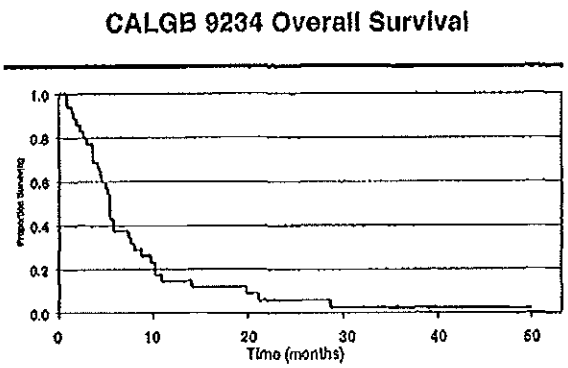

Figure 1. Overall survival for malignant mesothelioma patients treated with high-dose paclitaxel.

to be terminated and it would be concluded that the new regimen was not worth further investigation.

Results

Patient characteristics

Demographic and exposure characteristics for 35 patients are outlined in Table 1. Age, sex, tobacco, and asbestos exposure were consistent with earlier CALGB cohorts of patients. The performance status (PS) of this group of patients was worse than earlier CALGB cohorts with 10 patients (29%) being PS 2 [9]. Time from symptoms to diagnosis was generally less than six months, comparable to other studies. Over 50% of patients had nodal involvement or local extension into liver or bone at the time of study entry. The median time from diagnosis to on study was 1.1 months (range 0.03–61.0).

Response, failure-free survival, sites of failure and survival

The median number of cycles was three (range 1–18), with 24 (69%) patients receiving four or fewer cycles. A total of 137 cycles were administered to the 35 patients. Thirty of the thirty-five patients were evaluable for disease response. The five patients who were not evaluable for response included one patient who died on day 18 of pneumonia without ever having experienced leukopenia, three patients who experienced rapid declines in performance status after one dose and who did not undergo repeat imaging before going off study, and one patient who left the country to pursue alternative therapy. There were no complete responses. Three patients had regression of evaluable disease (9%; 95% confidence interval (95% CI): 2%–23%), and 19 patients had stable disease (54%). The durations of partial response/regression were 4, 6 and 7+ months. The 7+ month regressor developed grade 3 motor and sensory neuropathy and after 10 cycles, stopped paclitaxel. He then received radiation therapy to the known disease before progressing at 14 months. The median failure-free survival was three months (95% CI: 1.7–14.1 months). The Kaplan–Meier plot of survival time is presented in Table 2. The median

Table 1. Paclitaxel plus G-CSF phase II trial in mesothelioma: Patient characteristics.

Characteristics	Number of patients (%)
Demographics	
Age	
40–49	4 (11%)
50–59	10 (29%)
60–69	12 (34%)
70+	9 (26%)
Mean (SD)	61.5 (9.9)
Sex	
Female	4 (11%)
Male	31 (89%)
Race	
White	35 (100%)
Black	0 (0%)
Exposure to possible carcinogens	
Tobacco	
No/unknown	12 (34%)
Yes	23 (66%)
Asbestos	
No	8 (23%)
Yes	23 (66%)
Unknown	4 (11%)
Selected clinical data at entry	
Performance status	
0 – fully active	5 (14%)
1 – ambulatory	20 (57%)
2 – bed < 50% of the time	10 (60%)
Chest pain	
No	14 (40%)
Yes	21 (60%)
Dyspnea	
No	6 (17%)
Yes	28 (80%)
Unknown	1 (3%)
Duration of symptoms prior to diagnosis	
Less than three months	12 (34%)
Three to six months	13 (37%)
More than six months	10 (29%)
Weight loss in previous six months	
None or < 5% of body weight	17 (49%)
5%–10%	12 (34%)
> 10%	6 (17%)
Central assessment of cell type (histology)	
Epithelial	23 (74%)
Mixed	2 (7%)
Sarcomatous	6 (19%)
Platelet count (/μl)	
> 400,000	21 (60%)
⩽400,000	14 (40%)
Serum CEA level (ng/ml)	
Not done	8 (23%)
0–5.0	27 (77%)
> 5.0	0 (0%)
Site of disease at diagnosis	
Lung/pleura	34 (97%)
Peritoneum	1 (3%)
Nodes (any)	15 (43%)
Liver/bone/other	6 (17%)

survival time was 5.0 months (95% CI: 1.9–9.6). The two year survival was 6%.

We analyzed the sites of tumor involvement at the time of failure and found that progressive disease occurred locally in 20 (57%), locally and distantly in 2 (6%), distantly in 3 (9%) and at unknown or unspecified sites in 10 (28%).

Toxicity

Forty percent of patients experienced grade 4 granulocytopenia but there were no lethal episodes of neutropenic fever. Infections occurred in 17% of patients, one of which was fatal. Peripheral neurologic toxicity occurred in 11% of patients, and fatigue and malaise in 18%. Grade 2 anemia was seen in 54% of patients.

Discussion

Systemic therapy for malignant mesothelioma remains disappointing with no single agent or combination of agents displaying sufficient activity to be considered as 'standard of care'. For this reason the CALGB has pursued studies of new agents. In this phase II study only minor therapeutic efficacy of high-dose paclitaxel against mesothelioma was evident. The median survival of mesothelioma patients in sequential CALGB single agent phase II studies was seven months [9], and in that analysis the median survival of these paclitaxel treated patients was statistically inferior to other patients. It is likely that this poor survival is related to the large percentage (29%) of performance status 2 patients. Since no phase III studies have been performed in mesothelioma comparing the survival of patients treated with various types of systemic therapy compared to no systemic therapy, the survival of 'untreated' mesothelioma can only be inferred from retrospective studies. Such studies suggest a median survival of five to six months [1, 10]. The observations of the short time to treatment failure and five month median survival with paclitaxel suggests either no impact from paclitaxel in mesothelioma or a minor impact in a group of poor prognostic patients.

The EORTC saw no responders to single agent paclitaxel although the median survival of their patients was nine months [11]. Furthermore, other plant alkaloid-derived antineoplastic agents have demonstrated little to no activity against mesothelioma [1, 11]. Thus these negative results are not surprising. Both cisplatin and paclitaxel are active against human malignant mesothelioma xenografts and the combination appears to be at least additive if not synergistic [12]. Given the potential clinical synergism of carboplatin/paclitaxel, and the 'platelet-sparing' effect of the combination [13], there may be some benefit in pursuing taxane-platinum combinations for malignant mesothelioma.

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*Appendix

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