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Phase II Trial of Mitomycin-C in Patients with Small Cell Carcinoma of the Lung after Failure on Combination Chemotherapy

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Abstract—*Mitomycin-C was evaluated in a disease-oriented phase II trial in patients with small cell lung cancer who had failed prior conventional chemotherapy. The drug was given as a direct i.v. injection of* 15 mg/m² *repeated every* 6 weeks. *No objective tumor response was observed among* 15 *evaluable patients. This precludes a* 20% *level of activity with* 95% *confidence. Leukopenia* (60% *of patients) and thrombocytopenia* (20% *of patients) were common-effects observed. One patient developed a microangiopathic hemolytic anemia after a total mitomycin-C dose of* 42 mg. *We conclude that mitomycin-C in this dose and schedule is an inactive agent in previously treated patients with small cell lung cancer.*

INTRODUCTION

MITOMYCIN-C has not received adequate evaluation in small cell lung cancer. Therefore the Swiss Group for Clinical Cancer Research (SAKK) decided to evaluate mitomycin-C in a disease-oriented phase II trial in patients with advanced small cell lung cancer who had failed prior conventional chemotherapy.

MATERIALS AND METHODS

Between June 1981 and February 1983 21 patients with histologically or cytologically proven small cell lung cancer no longer amenable to conventional therapeutic measures were included in the trial. Eligibility criteria included measurable (two perpendicular diameters) or evaluable (one diameter) disease, provided that the sites had not received prior irradiation and had no recent chemotherapy (≥3 weeks, ≥6 weeks for nitrosoureas); satisfactory hematology (evidence of hematologic recovery from previous therapy with a WBC ≥3500/μl, a platelet count ≥100,000/μl) and biochemistry (serum creatinine ≤115 μmol/l and serum bilirubin ≤35 μmol/l) were also prereqisites. The initial work-up included a physical examination, blood chemistry and a chest X-ray. Additional radiological work-up and bone marrow biopsies were performed when indicated. Patients with disease confined to one hemithorax with or without mediastinal nodes and with or without ipsilateral supraclavicular nodes were staged as having limited disease. Disease beyond these confines was classified as extensive. During therapy WBC and platelet counts were performed weekly. A complete physical examination, hematological and biochemical work-up and a chest X-ray were performed every 3 weeks. In the absence of rapid disease progression the response to treatment was assessed for the first time after 6 weeks according to standard response criteria [1]: complete response (CR), disappearance of all known disease determined by two observations not less than four weeks apart; a partial response (PR), 50% or more decrease in total tumor size of the lesions measured to determine the effect of therapy by two observations not less than 4 weeks apart without appearance of new lesions or

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progression of any lesion; no change (NC), a 50% decrease in total tumor size cannot be established nor has a 25% increase in the size of one or more measurable lesions been demonstrated; progressive disease (P), a 25% or more increase in the size of one or more measurable lesions or the appearance of new lesions.

Mitomycin-C was administered i.v. at an initial dose of 15 mg/m^2. The treatment was repeated every 6 weeks if full hematological recovery had occurred (WBC $\geq$3500/μl, platelet count $\geq$100,000/μl). Otherwise treatment was delayed for 1–2 weeks. If at this time the counts had not risen to normal values, the dose of mitomycin-C was reduced by 50%.

Pretreatment patient characteristics are shown in Table 1. All patients had failed one or more chemotherapy regimens. Nine patient had also received thoracic irradiation. All but two patients were ambulatory (performance status $\leq$2 according to WHO criteria [1]). The majority of patients had extensive disease with metastatic sites listed in Table 1. The median time between the original diagnosis and entry into the trial was 10 months (4–26 months).

Table 1. Patient characteristics

No. of patients	21	
Median age in yr (range)	61 (39–71)	
Sex		
Male	21	
Female	0	
Performance status (WHO)		
0–1	10	
2	9	
3	2	
Previous therapy		
None	0	
Radiotherapy:	19	
CNS prophylaxis		10
thoracic irradiation		4
CNS prophylaxis and thoracic irradiation		5
Chemotherapy	21	
3 drugs		4
4–6 drugs		11
>6 drugs		6
Stage of disease		
Limited	4	
Extensive	17	
Metastatic sites		
Chest only	3	
Liver	7	
Bone	6	
Bone marrow	1	
Peripheral nodes	5	
Skin	1	
CNS	3	
Median time interval in months	10 (4–26)	

RESULTS

Six of 21 patients entered in the trial died before day 42 without evidence of toxicity or clear-cut disease progression. These patients were classified as early non-toxic deaths. All of these patients had extensive disease and five of six patients had a performance status of 2 or 3. Fifteen patients were fully evaluable for response and toxicity. No complete or partial tumor responses were observed. Three patients with limited disease and a good performance status (0–1) had stable disease for 58+, 147 and 153 days respectively. Twelve patients had evidence of disease progression within 42 days after beginning treatment. Median survival was 91 days (range 28–263 days).

The major side-effect of mitomycin-C was myelosuppression. Nine of 15 patients had a leukocyte nadir <4000/μl (median leukocyte nadir 3500/μl, range 600–7900/μl). Three patients had a platelet count <100,000/μl (median platelet nadir 142,000/μl, range 13,000–300,000/μl). No episodes of bleeding or infection occurred during the treatment. The median hemoglobin nadir was 10.9 g/dl (range 7.6–14.8 g/dl). No patient suffered from nausea or vomiting and no patient had evidence of renal toxicity. No patient exhibited clinical or radiological findings suggesting pulmonary toxicity of mitomycin-C. One patient developed a hemolytic anemia on day 106 after two doses of mitomycin-C (total dose of 42 mg). The hemoglobin fell within 6 weeks by 2 g/dl to 8.9 g/dl. At this time the free serum hemoglobin was 7 mg/dl, the haptoglobin 0.26 g/l (normal range of 0.5–2.9 g/l) and the LDH 263 IU/l (upper limit of normal 190 IU/l). The patient exhibited a hemosiderinuria. The platelets were 80,000/μl. The serum creatinine remained normal. The patient went off-study for rapidly progressing disease on day 146. At this point of time the hemoglobin had risen to a value of 11.3 g/dl, whereas the platelets had fallen to 52,000/μl. The patient remained thrombocytopenic, with platelet counts between 52,000 and 88,000/μl. He died on day 248 due to progressive disease. It was felt that these findings were compatible with a microangiopathic hemolytic anemia, probably related to the mitomycin-C treatment.

DISCUSSION

Mitomycin-C was evaluated in a disease-oriented phase II trial in 21 patients with small cell lung cancer relapsing after primary therapy. In 15 fully evaluable patients no objective tumor responses were noted. This precludes a 20% level

of activity with 95% confidence. The lack of antitumor activity in this study is disappointing and different from the 60% rate of effectiveness reported by Sakura and co-workers [2]. In the latter report mitomycin-C was combined with a lysosome labilizer and it may well be that this agent enhanced the activity of mitomycin-C. Furthermore, in the Japanese trial no standard response criteria were used and pretreatment characteristics of the patients were not detailed. It is conceivable that the intensive prior treatment and the advanced stage of disease in most of our patients influenced the susceptibility to the subsequent therapy with mitomycin-C.

We conclude that mitomycin-C in the present dose and schedule has no antitumor activity in patients with small cell lung cancer who have failed or relapsed from primary chemotherapy.

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