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Short communication

Phase-II study of vindesine and hexamethylmelamine in patients with relapsing small cell carcinoma of the lung

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Summary. *Twenty-five patients with measurable small cell lung cancer relapsing after first-line chemotherapy were treated with vindesine 3 mg/m² IV on days 1 and 8 and hexamethylmelamine 100 mg/m² PO on days 1–14, repeated every 3 weeks. Among 18 fully evaluable patients there was 1 partial remission lasting for 111 days. Two patients had disease stabilization for 127 and 152 days, respectively. Fifteen patients had disease progression. The treatment was well tolerated, myelosuppression being the major side-effect.*

Introduction

Although small cell lung cancer is very responsive to a wide variety of treatments the majority of patients relapse after primary therapy and ultimately succumb to their disease. Results of salvage treatment after relapse have been disappointing. Vindesine is a semisynthetic vinca alkaloid, with known activity in patients with advanced small cell carcinoma of the lung who have failed prior conventional chemotherapy [4, 5]. Hexamethylmelamine is a triazine, which has been shown to have activity in small cell lung cancer [1, 3]. The mechanism of action of hexamethylmelamine has not yet been clearly defined. It is of interest that hexamethylmelamine has been demonstrated to be active in patients resistant to alkylating agents [2, 3]. On the basis of these data the Swiss Group for Clinical Cancer Research has evaluated the combination of vindesine and hexamethylmelamine in a phase-II trial in patients with small cell lung cancer who had failed conventional chemotherapy.

Materials and methods

The characteristics of the patients treated are summarized in Table 1. The diagnosis was confirmed by histology or cytology in every case. Seven patients were excluded from further analysis: one patient was ineligible for the trial (no measurable disease), two patients died early without evidence of toxicity or rapid disease progression, three patients developed central nervous system involvement before response assessment, and one patient refused further treatment after the first injection of vindesine. All patients but one were ambulatory and all patients had received extensive prior treatment. The majority of patients had extensive disease, with the metastatic sites listed in Table 1.

Vindesine 3 mg/m² was given by IV injection on days 1 and 8, and repeated every 3 weeks. Hexamethylmelamine was administered in a daily oral dose of 100 mg/m² on day 1–14 and repeated every 3 weeks. The doses were adjusted according to hematological values on days 1 and 8: full doses were given if the WBC and platelet count were above 3,500/µl and 100,000/µl, respectively. The doses were reduced by 50%

Table 1. Patient characteristics

Number of patients	25
Sex	
Male	22
Female	3
Median age in years (range)	60 (32–76)
Median time from initial diagnosis to study entry in months (range)	10 (4–24)
Performance status	
0	3
1	11
2	10
3	1
Prior therapy	
Radiotherapy	
CNS prophylaxis	14
Thoracic	11
Chemotherapy	
3 drugs	4
4–6 drugs	19
> 6 drugs	2
Stage	
Limited disease	7
Extensive disease	18
Metastatic sites	
Chest only	7
Liver	10
Bone	7
Bone marrow	2
Peripheral lymph nodes	3
Skin	2
CNS	2

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for a WBC of 2,500–3,500 and a platelet count between 70,000 and 100,000/μl. Treatment was delayed by 1 week if the WBC was < 2,500 and the platelet count < 70,000/μl. In the absence of rapidly progressing disease the response to treatment was assessed for the first time after 6 weeks, according to standard response criteria [6]. Remission duration and survival were calculated from day 1 of treatment.

Results

Eighteen patients were fully evaluable for response and toxicity. One partial remission lasting for 111 days was observed in a 61-year-old white man with extensive disease (metastases to bone, bone marrow, liver, and peripheral lymph nodes) and a performance status of 2. Two patients, one each with limited and extensive disease, achieved disease stabilization for 127 and 152 days, respectively. In 15 patients there was uninterrupted disease progression. Median survival for all patients was 103 days (59–221 days). The patients with partial remission and disease stabilization survived for 165, 202, and 221 days, whereas the median survival for patients with disease progression was 84 days (59–177 days).

Side-effects were mild. Of the 18 evaluable patients, 11 had a WBC nadir below 4,000/μl (median WBC nadir 3,500/μl, range 1,700–10,500/μl); 7 patients had normal platelet counts throughout the trial (> 100,000/μl), whereas one patient had a platelet nadir of 84,000/μl. Eight patients complained of mild gastrointestinal disturbances (WHO grade 1–2). Three patients developed signs of mild peripheral neuropathy (WHO grade 1), and in three patients neurotoxicity was moderate (WHO grade 2). One patient developed mild myalgias and one, mucositis.

Discussion

We have evaluated the combination of vindesine and hexamethylmelamine in a phase-II trial in 18 fully evaluable patients with small cell lung cancer relapsing after primary therapy. Only one partial remission was noted, giving a response rate of 6%. The 95% confidence interval for the true response rate is 1%–18%. We must therefore conclude that in the dose and schedule used, the combination of vindesine and hexamethylmelamine has little activity as salvage treatment in patients with small cell lung cancer relapsing after primary therapy.

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