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High-dose Cyclophosphamide and High-dose VP 16–213 for Recurrent or Refractory Small Cell Lung Cancer. A Phase II Study

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Abstract—*In nine patients with recurrent or refractory small cell lung cancer a phase II study with high-dose cyclophosphamide and high-dose VP 16–213 with autologous bone marrow transplantation was performed. The regimen used was based on a previously reported phase I study. In eight of the nine evaluable patients a response was seen (six PR and two CR). One patient died of treatment related toxicity. Infection is the most important toxicity. The response duration was short. This combination is a suitable 'late intensification' regimen for patients with minimal residual disease after standard dose induction chemotherapy.*

INTRODUCTION

STUDIES in animal tumor systems have shown a steep dose–response relationship for a variety of cytostatic drugs [1, 2]. The clinical equivalent of these experiments is found in the increased cure rate since the introduction of high-dose chemotherapy for lymphoma and leukemia [3, 4]. Also, for small cell lung cancer (SCLC) there seems to be a dose–response relationship for some drugs. Cohen *et al.* [5] found a considerable improvement of both response rate and median survival after increasing the doses of drugs used in a combination regimen, although the initial as well as the increased dose levels in this study now fall in the low-to-standard dose range. Two of the most active drugs against SCLC, cyclophosphamide and VP 16–213, have at standard dose levels a response rate of approximately 40% [6, 7]. At much higher dose levels the response rates increase to 84% for cyclophosphamide [8] and 80% for VP 16–213 [9]. These observations support the existence of a dose–response relationship for these drugs over a wide range of dosages in patients with SCLC.

Previously we described the results of a phase I study with high-dose cyclophosphamide together with increasing doses of VP 16–213 and autologous bone marrow transplantation (ABMT) in patients with solid tumors [10]. The dose-limiting toxicity of this combination was mucositis of the oropharyngeal region at dosages of cyclophosphamide of 7 g/m^2 and VP 16–213 of 2.5 g/m^2. Acceptable toxicity was seen at dosages of 7 g/m^2 and 1.5 g/m^2 respectively; for older patients (>50 yr) a VP 16–213 dose of 0.9 g/m^2 was considered to be tolerable.

In this report we describe the results of a phase II study with this combination regimen and ABMT in patients with SCLC.

MATERIALS AND METHODS

Patients

Pertinent data on nine patients with recurrent or refractory SCLC entering the study are given in Table 1. Entry criteria were age ≤ 65 yr, Karnofsky score ≥ 60, bilirubin levels ≤ 25 mmol/l, serum creatinine levels ≤ 150 μmol/l, leucocytes ≥ 3.0 × 10^9/l, platelets ≥ 100 × 10^9/l and no signs of tumor invasion in bilateral iliac crest biopsies and bone marrow smears.

All patients had measurable tumor localizations, not previously irradiated.

Informed consent was obtained from all patients and the study was approved by the local medical ethical committee.

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Table 1. Patient characteristics

Patient No.	Age/sex	Previous therapy (total dose in mg)	Response to previous therapy	Time between end of initial therapy and relapse (in months)
1	55/M	CTX (3000), CDDP (300), VP (6600), ADM (240), VCR (8), PCZ (4000), PCI 30 Gy, XRT 30 Gy	CR	12
2	59/M	CTX (5200), CDDP (520), VP (2400)	CR	1
3	52/M	CTX (6800), CDDP (680), VP (2400), PCI 30 Gy	CR	6
4	39/M	CTX (5600), CDDP (560), VP (2400)	PR	2
5	47/M	CTX (6400), CDDP (640), VP (2400), VDS (11.1)	PR	1
6	37/F	CTX (5600), CDDP (560), VP (2400), PCI 30 Gy	CR	3.5
7	52/M	CTX (6000), CDDP (600), VP (7800), PCI 30 Gy	CR	11
8	56/M	CTX (8500), ADM (375), VP (3000), PCI 30 Gy	CR	4.5
9	35/M	CTX (5600), CDDP (560), VP (2400), PCI 30 Gy	CR	9

Abbreviations: CTX = cyclophosphamide; CDDP = *cis*platinum; VP = VP 16–213; ADM = adriamycin; VCR = vincristine; PCZ = procarbazin; PCI = prophylactic cranial irradiation; XRT = radiotherapy to primary tumor; VDS = vindesine.

Bone marrow aspiration

Bone marrow aspiration, storage and reinfusion were performed as described previously [10, 11].

Cytostatic treatment

All patients received cyclophosphamide 7 g/m^2. One-third of the total dose, dissolved in 500 ml normal saline, was given as a 30-min infusion on three consecutive days. Mesna was given on the same days in a total dose of 4 g/m^2 in order to prevent hemorrhagic cystitis.

VP 16–213 was dissolved in 500 ml normal saline and given in 2 × 1-hr infusions with a 12-hr interval on the same days as cyclophosphamide. Patients ≤ 50 yr received 1.5 g/m^2 total dose, older patients 0.9 g/m^2.

After evaluation of the response on high-dose chemotherapy patients 2, 4, 5, 6, 7, 8 and 9 received radiotherapy on the site of the major tumor bulk. Patient 3 subsequently received four courses of high-dose VP 16–213 (1.5 g/m^2).

Toxicity was graded according to WHO criteria [12].

Supportive care

Patients were treated in a single-person bedroom. Intravenous therapy was given through a central venous Hickman catheter. Nutritional support consisted of 4000 kcal/day given either totally parenterally or as a combination of oral and parenteral feeding. All patients received prophylactic antibiotics directed against potential pathogenic flora in the digestive tract [13]. This regimen consisted of amphotericin B 4 × 500 mg orally and lozenges (6 × 10 mg), polymyxin B 4 × 200 mg and cotrimoxazole 3 × 2 tablets (each tablet contained 80 mg trimethoprim and 400 mg sulfamethoxazole).

Prophylactic platelet transfusions were given at a thrombocyte level of ≤15 × 10^9/l.

In case of an infection, defined as temperature ≥ 38°C (axillary) and clinical or bacteriological signs of an infection, first-line antibiotic treatment consisted of a combination of cefuroxim and tobramycin.

Response

The response was evaluated 4 weeks after the start of treatment. Complete response (CR) was defined as disappearance of all known tumor lesions. Partial response (PR) was defined as a decrease of more than 50% of the product of the largest perpendicular diameters of all measurable lesions. Stable disease (SD) was defined as a less than 50% regression without signs of progression. Progression was defined as an increase over 25% of a measurable lesion or appearance of new tumor lesions. Toxic death (TD) was defined as death due to treatment related toxicity.

Response duration and survival time were measured from the first day of high-dose chemotherapy.

RESULTS

Tumor response

Eight out of nine patients were evaluable for response. Two patients had a CR, six a PR (Table 2). One patient died on day 15 due to treatment-related toxicity; at autopsy no tumor was found. In one of the PR patients a CR of the brain metastases was seen.

The median response duration in the eight responding patients was 5 months (range 2–8+). The median survival was 6 months (range2+–12). Two patients are still alive without tumor progression.

Table 2. Results of high-dose chemotherapy

Patient No.	Response	Response duration (months)	Survival (months)
1	TD	—	—
2	PR	3.5	5
3	PR/CR	6	12
4	PR	7	9+
5	CR	6	8
6	CR	6	8
7	PR	2	3
8	PR	4+	4+
9	PR	3+	3+

Toxicity

All patients developed leuco- and thrombocytopenia (Table 3). There were no bleeding episodes, except one small gastrointestinal tract bleeding. In all patients fever due to an infection developed and in eight patients a causative microorganism was found; in patient 1 this was found at autopsy. In one patient Herpes simplex infection was suspected but not confirmed. During the 3 days of chemotherapy infusion all patients experienced nausea and vomiting, WHO grade 2–3. Some had at that time diarrhea grade 2; during cytopenia five patients had diarrhea, grade 2–4 (Table 3), in patient 9 *Candida* overgrowth was found in the gastrointestinal tract and in patient 4 *Clostridium difficile* toxin was present in the feces. Mucositis of the oropharyngeal region developed in all patients (Table 3). Skin toxicity was mild, grade 1. There were no signs of bladder toxicity.

DISCUSSION

Although SCLC is a tumor with a high response rate, after standard-dose chemotherapy, often resulting in complete clinical remissions, only a minority of the patients will have a long-term disease-free survival. The response rate of second-line chemotherapy for progressive or relapsing SCLC is low, therefore new treatment modalities, as, for instance, high-dose chemotherapy, have to be investigated.

In this study we used a combination of high-dose cyclophosphamide and high-dose VP 16–213 with ABMT based on the results of a previously described phase I study [10]. Both drugs are among the most active against SCLC at standard dose levels, and furthermore for both drugs a dose–response relationship for SCLC exists.

This is an aggressive regimen with considerable toxicity. Overall the treatment was tolerated well, which might have been influenced by the relatively young patients. In the previous phase I study we described severe toxicity of this regimen, especially in older patients. The major disadvantage of this treatment modality is the high incidence of serious, mainly Gram-positive, infections. In the study presented now a response rate of 100% is seen and, although it is only in a small group of patients, it can be predicted that it will be an active combination with a >50% response rate in a larger group of comparable patients within 95% confidence limits.

The high response rate in this group of patients might have been influenced by the selection of the patients, because seven patients had apparently very sensitive tumors regarding the CR after standard chemotherapy. On the other hand, the response improvement in the two patients with only a partial remission after the induction regimen supports the presumed dose–response relationship for both drugs. In this way it might be possible to overcome to some degree the presumed existence of either primary or induced drug resistance. The latter might have been the case since both drugs were used in the initial treatment.

The main potential for the application of this regimen is its use as a 'late intensification' to eliminate minimal residual disease. The patients who could with this treatment strategy possibly become curable are those who are in complete

Table 3. Toxicity

Patient No.	No. of days with leucocytes $\leq 0.5 \times 10^9/l$	No. of days with leucocytes $\leq 1.0 \times 10^9/l$	No. of platelet transfusions	Mucositis (WHO grading [12])	Diarrhea during cytopenic phase (WHO grading [12])
1	12+	12+	3	1	1
2	10	12	3	0	0–1
3	13	14	5	1	3–4
4	13	14	5	1	2
5	15	17	5	2	3
6	13	14	8	3	3–4
7	20	21	4	1	0
8	14	15	4	1	0
9	13	14	4	4	4

clinical remission after standard chemotherapy. At that moment marrow is harvested and reinfused after ablative chemotherapy.

This strategy is supported by the mathematical model of Norton and Simon [14]. In this situation the bone marrow reserve capacity is still sufficient with respect to the number of bone marrow CFU_cs [15]. Furthermore, the risk of bone marrow involvement by tumor cells is minimal due to the 'clean-up' by the standard therapy.

The treatment of SCLC patients with persistent or progressive tumors with this high-dose regimen is not justifiable considering its high morbidity and short response duration. The addition of new active myelotoxic drugs to cyclophosphamide and VP 16–213 might, however, yet improve the response duration in these patients.

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