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ORIGINAL ARTICLE

Dexamethasone, cyclophosphamide, etoposide and cisplatin (DCEP) for relapsed or refractory multiple myeloma patients

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Summary

Purpose: *The purpose of this study was to assess the efficacy and toxicity of DCEP (dexamethasone, cyclophosphamide, etoposide, cisplatin), as third-line regimen in relapsed or refractory multiple myeloma (MM) patients.*

Patients and methods: *Twelve patients (11 men, 1 woman, aged 38-73 years, median 58) with relapsed or refractory MM received 28 cycles of DCEP. Eleven out of 12 patients had already failed 4-6 cycles of VAD (vincristine, doxorubicin, dexamethasone), 7/12 had received 2 or more lines of prior therapy and one of them had high-dose therapy with stem cell support. Seven out of 12 patients were candidates for megatherapy with autologous peripheral blood stem cells transplantation (ASCT) either as consolidation or as salvage treatment. Each cycle of DCEP consisted of cyclophosphamide 400 mg/m^2/daily, cisplatin 15 mg/m^2/daily and etoposide 40 mg/m^2/daily as a 24h infusion, all three drugs administered on days 1-4; plus dexamethasone i.v. bolus 40 mg daily, days 1-4. The dose of cisplatin was adjusted in case of renal impairment. G-CSF was administered daily from day +5 to recovery. The course was repeated every 28 days or was delayed 5-10 days according to the patient's clinical condition.*

Results: *The regimen was well tolerated with no major adverse reactions, except for grade 3 or 4 myelotoxicity of short duration. Responses were assessed using the EBMT criteria after the second cycle. Two out of 12 patients achieved complete remission (CR) and 5/12 partial remission (PR), while 5/12 had no response (NR). The overall response (OR) was 58.3% with a median response duration 9 months (range 4-36). Four patients proceeded to successful peripheral blood stem cell mobilization and transplantation.*

Conclusions: *DCEP is an effective and safe salvage treatment for relapsed or refractory MM patients which also offers the possibility for a successful peripheral blood stem cells collection in patients eligible for high-dose therapy and ASCT.*

Key words: autologous peripheral stem cell transplantation, DCEP, multiple myeloma, relapsed/refractory

Introduction

Multiple myeloma is an incurable disease even in young patients who can tolerate very aggressive therapeutic approaches, with the possible exception of allogeneic stem cell transplantation which may offer a possibility of cure of this debilitating disease [1]. Therefore the goal of treatment of MM is to achieve remission, improve the quality of life and prolong survival of the patients.

During the last two decades the first line treatment of MM consists of several cycles of the VAD regimen (vincristine, doxorubicin, dexamethasone) [2,3]. After a satisfactory remission eligible patients receive high-dose therapy followed by ASCT.

Drugs such as the rather recently introduced

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thalidomide and bortezomib are used as second-line options either to achieve a new response after a relapse or to maintain a plateau after a PR [4]. Thus, since a lot of patients are refractory to all described regimens and sooner or later practically patients present with a new relapse, further therapeutic options are needed.

DCEP (dexamethasone, cyclophosphamide, etoposide and cisplatin) is a regimen which is known to be effective in stem cell mobilization in MM patients [5-7] or as a part of consolidation therapy after ASCT [8,9]. In this paper we present its effectiveness and toxicity as an alternative regimen for patients with refractory or relapsed MM.

Patients and methods

Study design and patient eligibility

From March 2003 to February 2006, 12 patients (11 men and 1 woman, aged 38-73 years, median 58) with relapsed/refractory MM, not immediately eligible for autologous or allogeneic transplantation were treated in our institution with the DCEP regimen (total of 28 cycles). All patients' records were reviewed and data were collected and stored.

Side effects, response rate, early and late toxicities, progression-free survival (PFS), type of monoclonal protein, Salmon-Durie stage at the beginning of DCEP treatment, performance status and the number and nature of prior therapies were thoroughly recorded.

Patients with poor performance status and/or cardiopulmonary, renal, neurological and liver disease were not included. Patients older than 75 years were not eligible for treatment.

Relapse after response to chemotherapy, an inclusion criterion of this study, was defined as an increase of at least 25% in serum monoclonal protein or as a 100% increase in urine paraprotein from its lowest value, appearance of new skeletal lesions or increase in bone marrow cells by at least 25%.

Evaluations before treatment included medical history, physical examination, CBC, renal and liver function tests, serological markers for HBV, HCV, HIV, serum β2-microglobulin, CRP, albumin, serum and 24-hour urine protein electrophoresis and immunofixation, skeletal x-rays, skeletal CT scans and bone marrow aspirate and/or biopsy.

Treatment

The DCEP regimen consisted of dexamethasone 40 mg/day i.v. bolus, days 1-4. Cyclophosphamide 400 mg/m^2/day, plus etoposide 40 mg/m^2/day, plus cisplatin 15 mg/m^2/day (if serum creatinine < 1.5 mg/dl), mixed in a 1 L bag of normal saline were infused over 24 hours, days 1-4. Cisplatin doses were modified according to renal function as follows: if serum creatinine was 1.6-2.0 mg/dl cisplatin dose was reduced to 10 mg/m^2, if it was 2.1-3.0 mg/dl the dose was reduced to 7.5 mg/m^2 and no cisplatin was administered if serum creatinine was above 3.0 mg/dl.

Twenty-four hours after the completion of therapy, G-CSF was administered and continued until absolute neutrophil count (ANC) >2000/mm^3 for 2 consecutive days. Gastric prophylaxis was routinely administered either as H_2 antagonists or PPI inhibitors until the patient was discharged from the clinic, plus the usual medication against hyperurichemia etc. The course was repeated every 28 days or was delayed 5-10 days according to the patient's clinical condition.

Response and toxicity criteria

Response to therapy was evaluated after the second course of DCEP and was based on the EBMT criteria. CR was defined as disappearance of the monoclonal protein in serum and/or urine immunofixation, less than 5% plasma cells in the bone marrow and complete regression of extramedullary lesions if present. PR was defined as a greater than 50% reduction of serum myeloma protein and/or greater than 75% reduction of Bence-Jones protein, with >50% reduction of bone marrow plasma cells. The disease was considered stable (SD) when the serum monoclonal protein changes were <50% without additional complications of the myeloma. All other patients were rated as having progressive disease (PD). The duration of response was defined as the time interval between the documentation of response and the relapse of the disease, alike in patients who underwent ASCT as well as those who did not. Toxicity was graded according to the World Health Organization (WHO) criteria.

Results

The characteristics and clinical features of the 12 patients are listed in Table 1. Of note 50% of the patients were > 60 years old and 58% of the patients had received more than 2 lines of prior therapy and one of them had had high-dose therapy with stem cell support. In addition 7/12 (58%) had primary refractory disease or refractory relapse. All patients received

Table 1. Patient characteristics

Characteristic	*No. of patients*	*%*
Gender		
male	11	92
female	1	8
Age (years)		
median	58	
range	38-73	
>60	6	
Monoclonal protein		
G	9/12	76
A	1/12	8
D	1/12	8
Non secretory	1/12	8
Salmon-Durie stage		
I	3/12	25
II	9/12	75
Number of previous therapies		
1	5/12 1/5: MP 4/5: VAD	42
2	6/12 2/6: MP, VAD 2/6: VAD, thalidomide 2/6: VAD, bortezomib	50
3	1/12 MP, thalidomide, VAD	8
Previous high-dose therapy with ASCT	1/12	8
Disease status		
Primary refractory disease	4/12	33
Relapse	5/12	42
Refractory relapse	3/12	25

MP: melphalan - prezolon; VAD: vincristine - doxorubicin - dexamethasone; ASCT: autologous stem cell transplantation

Table 2. Results and toxicity of DCEP treatment

	Number of patients (n=12)	*%*
Complete response	2	17
Partial response	5	42
Stable and progressive disease	4	33
Overall response	7	58
Median duration of response (months)	9	
range	4-36	
Stem cell collection after DCEP	4/12	33
Toxicity (grade 3 - 4)		
neutropenia	7/28 cycles	25
thrombocytopenia	7/28 cycles	25

2-4 courses of DCEP and the response evaluation was done after the second course. Two out of 12 patients (16.7%) achieved CR and 5 out of 12 (41.6%) PR. OR was 58.3%. The median duration of response was 9 months (range 4-36). In 4 patients a successful peripheral blood stem cell collection after treatment was performed. Subsequently, these patients (one with refractory disease, one in CR and 2 in PR) underwent ASCT. The duration of response in the last 3 patients was 9, 10 and 12 months respectively, while the patient with refractory disease at transplantation achieved post-ASCT a PR of 4-month duration. Toxicity was low with grade 3-4 neutropenia and thrombocytopenia observed in 7/28 (25%) cycles. Three patients presented febrile neutropenia, while in 5 patients there was no toxicity at all. None of the patients presented significant renal or neurological toxicity and there was no death during treatment (Table 2).

Discussion

In our series DCEP was used as salvage chemotherapy for patients with refractory or relapsed MM who had already received several regimens. As it was mentioned 50% of the patients were >60 years old and 58% of the patients had received more than two lines of prior therapy and one of them had had high-dose therapy with stem cell support. It is worth noticing that 58% of them had refractory disease or refractory relapse. In addition, in 4/12 patients peripheral stem cells were mobilized and collected with satisfactory recruitment after the administration of DCEP, offering subsequently the opportunity to receive high-dose therapy with ACST as consolidation or salvage treatment. The regimen was well tolerated with no major adverse events. The median response duration of the whole group of patients was 9 months (range 4-36) and in transplanted patients 10 months (range 9-12).

The most common second-line regimens against MM are high dose dexamethasone, thalidomide, bortezomib and lenalidomide. High-dose dexamethasone provides response rates up to 20% [10]. Single-agent thalidomide 200-800 mg/day as salvage post-ASCT for MM has resulted in a total response rate of over 30%, but at least one third of the patients experienced constipation, weakness, fatigue, skin rash, peripheral neuropathy or somnolence [11]. Toxicity was dose-dependent. Therefore, lower dose of thalidomide has been combined with other conventional agents to improve response and reduce toxicity [12]. The proteasome inhibitor bortezomib, acting both on MM cells and the bone marrow microenvironment to overcome drug resistance achieves response rates of 40% [10]. In a multicenter, open–label, nonrandomized phase II trial, in which 202 patients with relapsed and refractory MM received 1.3 mg/m^2 of bortezomib twice weekly

for 2 weeks, followed by 1 week without treatment, for up to 8 cycles, the response rate was 35% and the median duration of response 12 months. In this trial grade 3 adverse events included thrombocytopenia (28%), fatigue (12%), peripheral neuropathy (12%) and neutropenia (11%). Grade 4 adverse events occurred in 14% of the patients [13]. A phase III clinical trial comparing bortezomib with dexamethasone for treatment of relapsed MM has shown a statistically significant prolongation of time to progression in the bortezomib-treated cohort. In the former study, the median time to progression after treatment with bortezomib was 7 months with 45% of patients achieving either CR or PR, vs. 5.6 months and 26%, respectively, for dexamethasone [10]. Combination of bortezomib with dexamethasone or other agents increases the response rate but the risk of adverse effects also rises [14-16].

Lenalidomide / revlimid (CC-5013), an analogue of thalidomide, has demonstrated significantly more potent and promising preclinical activity than thalidomide and has entered clinical trials [17, 18]. In relapsed or refractory relapsed MM patients it provides response rates of 25-28%, having a better adverse effects profile than thalidomide with myelosuppression as the major toxicity [19].

In our study toxicity was low. Grade 3-4 neutropenia and thrombocytopenia were observed in 7/28 (25%) cycles. Only 3 patients developed febrile neutropenia, while in 5 of 12 patients there was no toxicity at all. No significant renal or neurological toxicity was observed and there was no death during treatment.

As a conclusion, DCEP appears to be an effective salvage regimen for refractory or relapsed MM patients with an OR rate of 58.3%, which also offers the possibility for a successful peripheral stem cell collection. DCEP has a rather low toxicity profile and there was no treatment-related mortality. A certain disadvantage of the regimen is that the patient has to stay 15-20 days at the clinic, but this appears acceptable taking into account the general status of the patients and the benefits of the treatment.

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