Journal of BUON **13:** 193-197, 2008
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ORIGINAL ARTICLE

High dose chemotherapy and autologous stem cell transplantation in patients with multiple myeloma: the experience of a single haematological unit

X. Papanikolaou[1], D. Maltezas[1], P. Repousis[1], A. Athanassopoulos[2], S. Alexia[3], K. Megalakaki[1], M. Kotsopoulou[1], C. Mitsouli-Mentzikof[1]

[1]*Department of Haematology,* [2]*Unit of Haemapheresis,* [3]*Laboratory of Haematology, "Metaxa" Cancer Hospital, Piraeus, Greece*

Summary

Purpose: *To study the toxicity of high dose chemotherapy (HDCT) in multiple myeloma (MM) patients and its impact on event free survival (EFS) and overall survival (OS), and also the impact of thalidomide maintenance therapy on EFS and OS after HDCT.*

Patients and methods: *From April 1999 to November 2006 37 patients (29 males, 8 females) out of a total of 38 scheduled were treated with HDCT and autologous peripheral stem cell transplantation (APSCT), as consolidation treatment after first- or second-line chemotherapy. Their median age was 55 years (range 38-71). HDCT regimen used was melphalan 200 mg/m^2. Following HDCT thalidomide 100 mg/day was administered as maintenance therapy to 28 patients in a random fashion.*

Results: *All patients tolerated well HDCT and APSCT. There was no treatment-related mortality. The median time interval for neutrophil recovery (>500/mm^3) was 10 days (range 8-20), while the median time interval for platelets to recover to >20.000/mm^3 was 14 days (range 9-32). Twenty (54%) patients achieved complete response (CR), 15 (40%) partial response (PR), and 2 (6%) stable disease (SD). Before receiving thalidomide as maintenance treatment 12 (42%) patients were in CR, while all the others, except one who had progressive disease (PD), were in PR. CR correlated with better EFS and probably OS. Thalidomide maintenance treatment correlated with better EFS.*

Conclusion: *In our series of patients HDCT appears to be a totally feasible, safe and without treatment-related mortality procedure, even in patients older than 60 years of age. It has a major impact in terms of CR achievement, which seems to strongly correlate with a prolonged EFS and OS. The use of thalidomide as a maintenance therapy induces a greater EFS which could possibly yield an improved OS.*

Key words: autologous peripheral stem cell transplantation, high dose chemotherapy, multiple myeloma, thalidomide maintenance treatment

Introduction

MM is the second most common haematological malignancy [1]. It is still an incurable disease and, if left untreated, the median life expectancy of stage 3 MM patients is less than a year. The introduction of alkylating agents and corticosteroids in the early 1960s offered an improvement in terms of OS and EFS. Over the next 3 decades additional chemotherapeutic drugs did not manage to improve OS.

In the early 1980s McElwain and Powles first reported that were able to overcome drug resistance and induce CR with HDCT in previously treated MM patients, thus achieving improved OS [2]. While the duration and severity of myelosuppression was discouraging, it could safely be overcome with bone marrow, and later, peripheral blood stem cell rescue.

HDCT with APSCT has been increasingly used in the past 20 years in MM patients and is being considered the treatment of choice for patients younger than 65 years [3].

In the present study we report our experience with

Correspondence to: Xenophon Papanikolaou, MD. 11, Irodotou Street, Maroussi, Athens 151 22, Greece. Tel: + 30 210 8052354, E-mail: xenopap@yahoo.gr, cmitsouli@yahoo.gr

Received 09-10-2007; Accepted 13-11-2007

HDCT and APSCT in MM patients. We evaluated the toxicity of HDCT in those patients and its impact on EFS and OS. In addition, we evaluated the impact of thalidomide maintenance therapy on EFS and OS after HDCT.

Patients and methods

From April of 1999 to November of 2006 37 patients out of a total of 38 scheduled (93.3%) with newly diagnosed MM were treated with HDCT and APSCT as consolidation therapy after first- or second-line chemotherapy. Excluded were patients older than 70 years, and patients with active infection or significant comorbidities such as liver failure, heart failure (left ventricular ejection fraction < 50%), respiratory failure and not MM-related renal failure. One patient who had failed to achieve a successful peripheral stem cell collection received maintenance therapy with interferon-α (INF-α) for about one year. Twenty-nine (78.3%) of them were males and 8 (21.7%) females. The median patients' age was 55 years (range 38-71). Eight patients were older than 60 years. Two patients had creatinine levels above 2.0 mg/dl (normal range 0.6-1.1). Stem cell mobilization was achieved in 14 patients with G-CSF alone, in 20 with cyclophosphamide (2 g/m^2) plus G-CSF, and in the remaining 3 with the DCEP regimen (dexamethasone, cyclophosphamide, etoposide, cisplatin) and G-CSF. The mobilization yielded a median value of CD34+ cells of 3.22×10^6/kg (range $2.15\text{-}14.42\times10^6$/kg). The HDCT regimen consisted of melphalan 200 mg/m^2 i.v. Prior to APSCT all patients received the VAD (vincristine, doxorubicin, dexamethasone) regimen (4-6 cycles), except 3 who failed to respond to VAD. Two of them were treated with DCEP and one with bortezomib 1.3 mg/m^2, days 1,4,8,11,21. Prior to APSCT 3 of the patients were in CR, 31 in PR and 3 were refractory to treatment according to the EBMT criteria [4]. Maintenance therapy consisted of thalidomide 100 mg/day. The patients' clinical and laboratory characteristics are described in Table 1.

Table 1. Patient characteristics (n=37)

Characteristic	*Patients, n*	*%*
Gender		
Male	29	78.3
Female	8	21.7
Age (years)		
Median (range)	55 (38-71)	
> 60	8	21.7
≤ 60	29	88.3
Monoclonal protein		
G	22	59.4
A	8	21.7
Non secretory	3	8.1
Free light chain	4	10.8
ISS stage at diagnosis		
I	8	21.7
II	19	51.3
III	10	27
Disease status prior to HDCT		
CR	3	8.1
PR	31	83.7
RD	3	8.1

ISS: International staging system, HDCT: high dose chemotherapy, CR: complete response, PR: partial response, RD: refractory disease

Response and toxicity criteria

Response to therapy was evaluated 3 months after the HDCT and APSCT, according to 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 conditions were rated as progressive disease (PD). The duration of response was defined as the time interval between documentation of response and disease relapse. Toxicity was graded according to the World Health Organization (WHO) criteria [5].

Statistical methods

All statistical tests were two-sided. The Yate's corrected x^2 test was used for the qualitative measurements and the t-test and the paired t-test for the quantitative ones. Survival curves were plotted according to the Kaplan-Meier method. Statistical significance was set to $p < 0.05$.

Results

All of the patients tolerated well the HDCT and APSCT. No death occurred during the phase of aplasia and no infectious complication was severe enough to require further treatment at the Intensive Care Unit. Febrile neutropenia (83.7% of the cases), and gastrointestinal toxicity were the major cause of morbidity

with 48.6% of the patients having severe (grade 3-4) mucositis. The median time of hospitalization was 16 days (range 10-45).

The median time interval for neutrophil recovery to > 500/mm^3 was 10 days (range 8-20), while the median time interval for platelets to recover to > 20,000/mm^3 was 14 days (range 9-32). Age and renal impairment were not negative predictive factors for the stem cell mobilization or the engraftment time interval.

The therapeutic result was evaluated 3 months after the HDCT. All 3 patients that were in CR prior to HDCT remained disease-free. Of the 31 patients that were in PR 17 (54.8%) achieved CR and 14 (45.1%) remained in PR, while improving further their remission. Of the 3 patients that were refractory to the treatment prior to the APSCT 2 achieved PR while one remained refractory. The type of paraprotein was of statistical importance in terms of achieving CR after APSCT in the group of patients who were in PR prior to HDCT (43.7% of IgG vs. 26.5% of IgA; $p < 0.01$). Results and toxicity are presented in Table 2.

After the HDCT, 28 out of 37 (75.6%) patients received thalidomide 100 mg/day as maintenance treatment, regardless of their remission status. Twelve (42%) of them were in CR while all the others, except one who had progressive disease, were in PR.

With a median follow up time of 40 months (range 2-81) 16 patients relapsed, while 6 of them were in CR (30% of the CR and 62.5% of the PR patients). The relapse rate of patients on thalidomide was 35.7% (10 patients); for those without thalidomide it was 66.5% (p=0.05). The median time to relapse was 15 months (range 4-54). Of the 16 patients who relapsed 7 eventually died, 2 are in CR after salvage therapy, 5 are in PR and 2 have refractory disease. The OS and EFS of the patients are presented in Figures 1 and 2.

Table 2. Response and toxicity of HDCT

	Patients	
	n	*%*
Response		
Complete response	20	54
Partial response	15	40
Stable and progressive disease	2	6
Overall response	35	94
Median EFS (months)	15	
Range	4-54	
Toxicity		
Febrile neutropenia	31	83.7
Grade 3-4 mucositis	18	48.6

EFS: event free survival

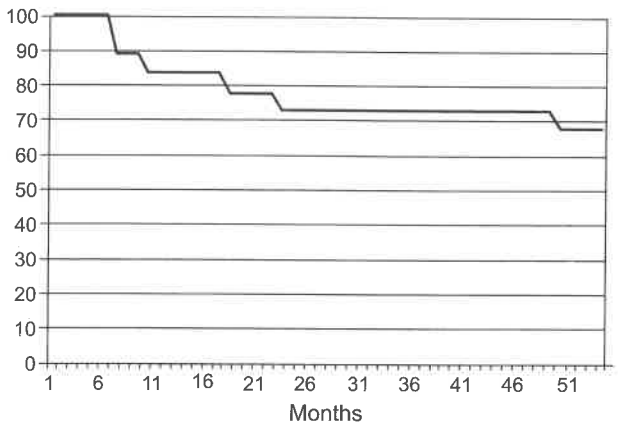


Figure 1. Overall survival.

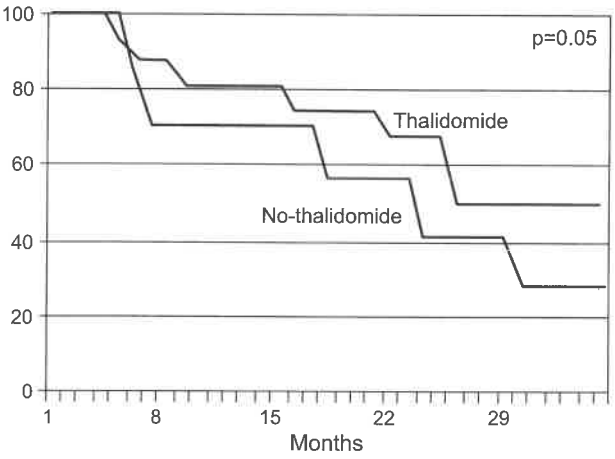


Figure 2. Disease free survival with or without maintenance with thalidomide.

Discussion

In our series of patients successful stem cell collection was feasible in 97% of the cases, regardless of their remission status or bone marrow plasma cell infiltration prior to the HDCT treatment. This fact clearly states that for patients younger than 70 years of age the intention to treat with HDCT and the actual treatment have no practical differences, thus excluding any selection bias which could falsely influence the interpretation of the outcomes and potential benefits of HDCT for a selective group of patients. Although past [6] and present [7] efforts were done to improve the standard conditioning regimen of HDCT used also in our clinic, none of them showed any clear improvement in OS. Consequently melphalan 200 mg/m^2 remains the gold standard for HDCT with peripheral stem cell rescue.

Although the treatment-related morbidity of HDCT was considerable, it did not result in any treat-

ment-related death, in accordance with results published in other series [8]. This statement holds also true for patients with renal impairment or older than 65 years old. The pharmacokinetics of intravenous melphalan are not influenced by creatinine clearance, and although there is a tendency for greater gastrointestinal toxicity, there is no impact on the quality of stem cell collection and/or engraftment, as stated by Badros et al. [9].

Three months after the APSCT 54% of our patients achieved CR, according to the EBMT criteria. The achievement of CR in this study proved a strong favorable predictive factor for prolonged EFS and OS. This is in accordance with most of the published trials [9-11]. In almost all randomized trials when one arm induces more CRs than the other, it also yields longer EFS which is usually associated with longer OS. The potential of HDCT to further increase the percent of CRs is stressed in most of the published series [9,10,12,13]. Comparing HDCT with conventional chemotherapy (CC), a clear advantage of HDCT in EFS and probably OS for patients < 65 years of age is seen, partly because HDCT increases the percentage of CRs. Only two recent trials (PETHEMA [14] and the US Intergroup study [15]) failed to demonstrate any survival benefit for MM patients aged < 70 years, although the EFS benefit was clear. The aforementioned studies enrolled a large number of patients but the PETHEMA study used HDCT as salvage treatment for the non-responders and patients with early relapse of the CC arm, which could imply a selection bias for the HDCT arm; the US Intergroup study included a large number of patients aged > 65 years, a subgroup of patients that HDCT is no longer the treatment of choice due to the fact of superiority of the regimens that incorporate newer drugs for MM, thus providing also a selection bias for ASCT [16,17]. In the former study, surprisingly enough, the two study arms had similar CR rates, a fact that is rather the exception than the rule in all the other studies.

In a recent large trial by Child et al. 407 patients were randomized to receive CC or HDCT. The median OS was significantly prolonged by almost a year in the HDCT arm (54 vs. 42 months). To date, this superiority has clearly been demonstrated in younger patients with a median age of 51 years [18]. For patients > 65 years Facon et al. demonstrated that MPT (melphalan, prednisolone, thalidomide) is superior in terms of OS than HDCT. Of note is the fact that the HDCT arm didn't receive any kind of maintenance treatment [16].

The fact that CR achievement does not always mean improved OS is especially true for the subgroup of patients with the t(4;14) chromosomal translocation and those that their MM emerged from a documented MGUS (monoclonal gammopathy of undetermined significance) [19].

Even when CR is achieved patients with MM will eventually relapse. In an effort to sustain remission various maintenance therapies have been evaluated in MM. INF-α and prednisolone failed to demonstrate any clear OS benefit. In our series thalidomide maintenance therapy was correlated with longer EFS. Due to the fact that the median survival has not yet been reached in our study and also that thalidomide was frequently used as salvage treatment in the no-maintenance group, we can not yet state the impact of thalidomide on OS. That comes in accordance with Barlogies' et al. latest findings [15]. Harouseau et al. [12] demonstrated also a survival benefit when thalidomide was used as a maintenance treatment after HDCT, a finding that is also confirmed by other studies too.

Novel agents for MM (bortezomib, thalidomide, lenalidomide) when used as upfront treatment have yielded impressive results in terms of CR and overall response [20-22]. Although this fact may imply the need for re-evaluation of HDCT therapy in MM, it does not necessarily exclude the potential role of HDCT as an upfront or salvage therapy. The follow up of the patients treated with HDCT is much more extended than the ones treated with the novel agents and the OS benefit is clear at least for the younger patients while the survival benefit of the newer agents remains to be confirmed in large randomized studies. In addition to that, HDCT does not exclude in any way the use of novel agents, either as induction or salvage treatments [17,21].

We conclude that in the present series of patients HDCT appears to be a totally feasible, safe and without treatment-related mortality procedure, even in patients older than 60 years of age. It has a major impact in terms of CR achievement, which seems to correlate strongly with prolonged EFS and OS. The use of thalidomide as a maintenance therapy induces a greater EFS, which could possibly yield an improved OS. Finally, although the exact role of HDCT in the treatment of MM remains to be fully determined, especially in the era of the novel agents, it is a powerful and safe weapon in the therapeutical inventory of the physician treating patients with MM.

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