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Results of a Retrospective Single Institution Analysis of Targeted Skeletal Radiotherapy with ^{166}Holmium-DOTMP as Conditioning Regimen for Autologous Stem Cell Transplant for Patients with Multiple Myeloma. Impact on Transplant Outcomes

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ABSTRACT

^{166}Holmium-DOTMP is a beta-emitting radiophosphonate that localizes specifically to the bone surfaces and can deliver high-dose radiation to the bone marrow. Phase I/II trials showed feasibility and tolerability when combined with high-dose melphalan with or without total-body irradiation (TBI) in patients with multiple myeloma (MM) undergoing autologous stem cell transplantation (ASCT). The purpose of this study was to define the potential impact of ^{166}Holmium-DOTMP on outcomes in patients with MM undergoing ASCT. Retrospective review of transplant outcomes among patients with MM who received an ASCT between January 1998 to December 2001 with either melphalan 200 mg/m^2 or a ^{166}Holmium-DOTMP containing regimen as part of their initial therapy. Univariate analysis was performed for response, overall survival (OS), and event free survival (EFS). One hundred four patients were identified, of which 41 received a ^{166}Holmium-DOTMP containing regimen and 63 received melphalan alone. The ^{166}Holmium-DOTMP patients were divided into 2 groups according to the dose received (<2400 mCi versus ≥2400mCi). The ^{166}Holmium-DOTMP group had a trend towards a higher complete remission (CR) rate compared to patients receiving melphalan alone (51% versus 32%). The median EFS for the low-dose ^{166}Holmium-DOTMP, the high-dose ^{166}Holmium-DOTMP, and melphalan alone was 30, 23, and 19 months, respectively; the OS rate at 5 years for the 3 groups was 61%, 40%, and 43%, respectively. ^{166}Holmium-DOTMP, in combination with high-dose melphalan, can result in higher CR rates when given in optimal doses (<2400 mCi) when compared to melphalan alone, and should be further tested in phase III trials in patients with MM undergoing ASCT.

KEY WORDS

High dose therapy • Myeloma • Autologous stem cell transplant • Targeted skeletal radiotherapy

INTRODUCTION

Multiple myeloma (MM) is a clonal B cell disorder, with a gradually progressive natural history and a median survival of 3 years [1]. Conventional doses of chemotherapy only rarely result in complete remission (CR); on the other hand, high-dose chemotherapy with autologous stem cell transplantation (ASCT) has been shown to improve complete remission (CR) rates, event free survival (EFS), and overall survival (OS) in selected patients, especially when performed early in the course of the disease [2,3]. High-dose melphalan, with or without total body irradiation (TBI), is the most commonly used

conditioning regimen leading to CR rates of up to 30% after a single ASCT [4,5].

Although MM is a radiosensitive malignancy, TBI has been shown to add toxicity without improving survival compared to patients treated with melphalan alone [6]. The main drawback of external beam radiation has been the toxicities associated with radiation of nontarget tissues, particularly the lung, liver, kidney, and nervous system [6,7]. Targeted radiotherapy resulting in localized delivery of radiation to the skeleton could allow substantial increases in radiation delivery to bone and bone marrow, whereas limiting the systemic toxicities observed with TBI. This approach has been made possible because of the development of bone-seeking radioisotopes that result from the chelation of radioisotopes with phosphonates that bind tightly to trabecular bone. These bone-seeking radioisotopes allow for delivery of substantial amounts of radiation to the bone and marrow space, and have been shown to be effective for palliative therapy of bone metastasis [8-11]. The experience with bone-seeking radioisotopes for palliative therapy of bone metastasis demonstrated that high doses of radiotherapy could be selectively and effectively delivered to the bone, sparing nontarget organs; the observation that myelosuppression was the most common toxicity also suggested the potential role of this therapeutic modality for treatment of malignant hematologic disorders of the bone marrow, and as part of high-dose therapy conditioning regimens [12-14].

Holmium-166 (^{166}Ho) is a beta-emitter with high energy (maximum effect 1.85 MeV) and a relatively short half-life of 26.8 hours. ^{166}Ho also has a minor gamma component, which allows for simultaneous imaging and dosimetry studies. In an effort to explore alternative ways to deliver radiotherapy along with the conditioning regimens, the radioactive agent ^{166}Ho was conjugated to the phosphonate ethylenediaminetetramethylenephosphonic acid (DOTMP). The compound ^{166}Ho-DOTMP was used in 1 phase I single-center study and 2 phase I/II multicenter studies in patients with MM receiving high-dose chemotherapy followed by ASCT, conducted at the University of Texas M.D. Anderson Cancer Center, Fred Hutchinson Cancer Research Center, and the University of Miami [15-17].

Patients treated in the setting of these trials have now been followed for an average of 4 years, and thus the potential impact of ^{166}Ho-DOTMP on long-term outcomes in patients with MM can be assessed. To evaluate the impact on remission rates and survival of ^{166}Ho-DOTMP containing conditioning regimens we performed a retrospective analysis of patients treated on any ^{166}Ho-DOTMP containing protocol and compared it to the outcomes of patients undergoing ASCT for MM with melphalan 200 mg/m^2 during the same time frame. Herein are the results of this analysis.

PATIENTS AND METHODS

Selection Criteria

Patients were selected for review from the University of Texas M.D. Anderson Cancer Center database if they fulfilled all of the following criteria: diagnosis of MM, treated with high-dose therapy followed by a single ASCT for either first remission consolidation or primary refractory disease between January 1998 and December 2001 and conditioned with either melphalan 200 mg/m^2 or a ^{166}Ho-DOTMP containing regimen.

Conditioning Regimen

Two different ^{166}Ho-DOTMP protocols were open during the time frame analyzed: protocol DM98-108 consisted of 800 cGy of TBI given as 4 daily 200-cGy fractions, together with 40 mg/m^2 melphalan and ^{166}Ho-DOTMP given at different doses targeted to deliver either 20, 30, or 40 Gy to the bone marrow, and protocol DM98-109, which consisted of 140 mg/m^2 or 200 mg/m^2 of melphalan plus ^{166}Ho-DOTMP, also given in escalating doses calculated to deliver 20, 30, or 40 cGy to the red marrow.

^{166}Ho-DOTMP therapy has been previously described in detail [16]. In brief, a therapy dose of ^{166}Ho-DOTMP was administered 7 to 10 days prior to the expected transplantation date, following dosimetric calculations, which were done using a tracer 30-mCi dose in each patient, to deliver an actual bone marrow dose of 20, 30, or 40 cGy. Melphalan was given as a single or 2-day course. Patients registered on Protocol DM98-108 also received TBI 800 cGy in 4 fractions. Eligibility for all trials were similar, with the exception that patients receiving ^{166}Ho-DOTMP together with TBI had to be $<$55 years of age; patients treated with high-dose melphalan alone during the study period did so because of patient or physician preference or lack of insurance approval to participate in the ^{166}Ho-DOTMP trials. All patients received standard posttransplantation supportive care according to institutional guidelines for ASCT. Protocols were institutionally approved, and all patients signed written informed consent. Approval for this retrospective study was obtained by the institutional review board as per institutional guidelines.

Response Criteria

The EBMT/ABMTR response criteria were used to assess response [18]. In brief, CR was defined as the complete disappearance of monoclonal protein from both serum and urine confirmed by 2 negative immune fixation studies performed at least 6 weeks apart

and <5% plasma cells in bone marrow biopsy. Partial response was defined as a >50% reduction of serum paraprotein and a >90% reduction in urine paraprotein for at least 6 weeks or a >50% reduction in bone marrow plasma cells in patients with nonsecretory myeloma. Relapse was confirmed by the reappearance of paraprotein by immunofixation or electrophoresis or by the worsening or the appearance of new lytic lesions, hypercalcemia, or plasmacytomas or a >25% increase in the level of serum or urine paraprotein in at least 2 distinct measurements.

Patients maintaining the same response status as in the pretransplant period were characterized as having achieved continuous CR (CCR) or continuous partial remission (CPR). Response was determined as the best response at 3 to 12 months posttransplant, and was based on the first of the 2 lowest consecutive paraprotein level estimations, regardless of the use of maintenance therapy and prior to any disease progression.

Statistical Analysis

For statistical analysis we defined 3 distinct groups of patients: patients who were conditioned with a ^{166}Ho-DOTMP containing protocol and received <2400 mCi (group A), patients who were conditioned with a ^{166}Ho-DOTMP containing protocol and received 2400 mCi or more (group B), and patients conditioned with melphalan 200 mg/m^2 only (group C). The dose of 2400 mCi represents the median ^{166}Ho-DOTMP dose delivered, and it was arbitrarily used to have an adequate number of patients in each group for statistical purposes.

Pretransplant patient characteristics were compared using the Kruskal-Wallis or the χ^2 tests for the numeric and the categoric variables, respectively. Statistical comparisons of response were based on the χ^2 test. Beta 2 microglobulin and albumin levels at the time of diagnosis were unavailable in 21 and 33 patients, respectively, and thus could not be analyzed in the univariate or multivariate analysis. Survival was estimated by the Kaplan-Meier method and compared using the log-rank test [19-21]. Analysis of survival was based on the proportional hazards regression model. The following parameters were analyzed in univariate fashion for effect on OS and EFS: age, Beta 2 microglobulin, albumin, International Staging System (ISS) [22], Durie-Salmon stage [23], immunoglobulin isotype, disease response to induction, and conditioning protocol. Analysis was performed using the SPSS v14.0 software.

RESULTS

Patient Characteristics

One hundred four patients were identified who fulfilled our criteria; 21 patients had received a conditioning regimen with a dose of ^{166}Ho-DOTMP of <2400 mCi (group A), 20 patients received a conditioning regimen with a dose of 2400 mCi or greater of ^{166}Ho-DOTMP (group B), and 63 received high-dose melphalan alone at a dose of 200 mg/m^2 (group C). Sixteen patients in the ^{166}Ho-DOTMP group also received 8 Gy TBI: 9 in group A, and 7 in group B. ^{166}Ho-DOTMP dose administered ranged from 460 to 4476 mCi. Patient characteristics are shown in detail in Table 1. In brief, there were no significant difference among the groups regarding median age and gender. There was a higher proportion of patients with IgA myeloma in the ^{166}Ho-DOTMP groups, and a higher proportion of patients with Durie Stage III disease in group C. Among patients in whom Beta 2 microglobulin and albumin values at diagnosis were available, Beta 2 microglobulin levels were similar in all 3 groups (3.15, 3.25, and 3.5 for groups A, B, and C, respectively), whereas albumin values were lower in group C. Because of the large number of missing

Table 1. *Patient Characteristics*

	Group A ^{166}Ho-DOTMP <2400 mCi	Group B ^{166}Ho-DOTMP ≥2400 mCi	Group C Melphalan 200 mg/m^2	*P*-value Group A versus Group C
No. of patients	**21**	**20**	**63**	
***Age median (years)**	**52.5 (45-61)**	**53 (36-64)**	**55.5 (35-69)**	**NS**
% Male	**57**	**75**	**62**	**NS**
% IgA	**33**	**40**	**14**	**.03**
% DS III at diagnosis	**43**	**55**	**67**	**.14**
β2M at SCT				
% <3.5 mg/L	**71**	**80**	**62**	**NS**
% ≥3.5 mg/L	**19**	**20**	**33**	
Albumin at SCT				
% <3.5 g/dL	**19**	**35**	**30**	**NS**
% ≥3.5 g/dL	**81**	**65**	**70**	
% Primary refractory	**38**	**25**	**26**	**NS**

DS indicates Durie Salmon; SCT, stem cell transplant.
*Kruskal-Wallis.

Table 2. *Response to Transplantation*

	Group A ^{166}Ho-DOTMP <2400 mCi	Group B ^{166}Ho-DOTMP ≥2400 mCi	Group C melphalan 200 mg/m^2	*P* Group A versus Group C
OR rate %	95	90	92	.5
CR rate %*	57	50	36	.08
Conversion to CR %	55	48	32	.04
PR rate %†	38	40	56	.13
NRM %	(1‡) 5	(4‡) 20	(2‡) 3.2	.8
Median OS in months	NR	31 (14-49)	52 (44-61)	
Median EFS in months	30 (4-57)	23 (1-30)	19 (10-29)	

CR indicates complete remission; OR, overall remission; PR, partial remission; OS, overall survival; EFS, event-free survival.
*CR + CCR.
†PR + CPR.
‡Number of patients.

values, no formal comparison regarding these variables was made.

Response

As of May 2005, the median follow-up was 43.7 months, ranging from 2.3 to 80 months. The patient with the short 2.3-month follow-up was an overseas patient who was lost to follow-up and was censored at the time of his last visit. Two patients were nonevaluable because of the lack of a second protein electrophoresis or immunofixation studies to confirm response, and were classified as nonresponders.

Table 2 summarizes transplant outcomes. Objective response (CR plus PR) was similar in the 3 groups (95%, 90%, and 92%). There was a trend towards a higher rate of conversion to CR in the ^{166}Ho-DOTMP-containing groups (55% and 48% versus 32%). Of note, 75% of patients with partial response and 25% of the primary refractory patients attained a CR in group A compared to 40% and 12%, respectively, in group C. Nonrelapse mortality (NRM) rates were similar for group A and group C and significantly less than the 20% observed in group B, who received the higher dose ^{166}Ho-DOTMP.

OS and EFS

Fourteen patients (67%) of the 21 treated in group A were alive at the time of the analysis, as well as 7 patients in group B, and 35 (56%) in group C. The median survival time, estimated by the Kaplan-Meier method, has not been reached for group A, whereas it is 31 months (range 14-49) for patients in group B, and 52 months (range 44-61) for patients in group C (Table 2) Although not statistically significant, the 5-year OS for patients in group A was superior to that in patients in groups B and C, as shown in Figure 1.

In the last follow-up, 9 patients (43%) from group A, 16 (80%) from group B, and 46 (73%) from group C have progressed. Of those, 6 patients from the first group, 9 from second group, and 26 from the third group have died. The median EFS was 30, 23, and 19 months, respectively.

Prognostic Factor Analysis

An elevated Beta 2 microglobulin level and ISS at SCT were the only 2 significant predictors of OS and progression-free survival on univariate analysis

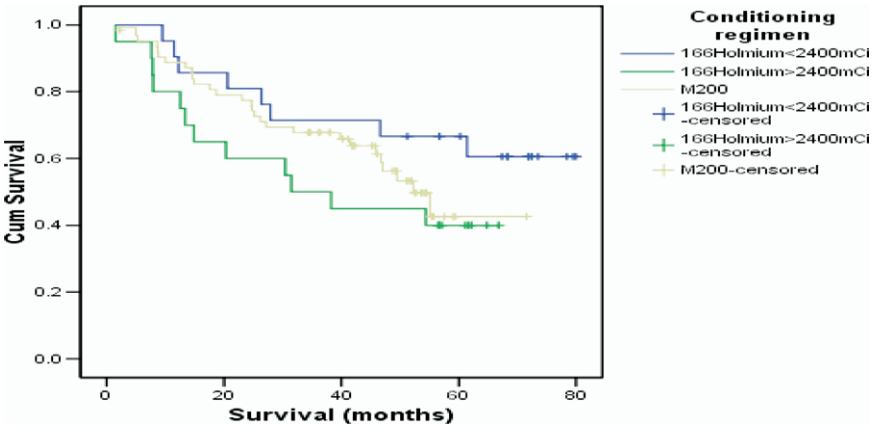

Figure 1. Overall survival.

(Table 3). Rates of failure were almost double in patients with Beta 2 microglobulin levels of 3.5 g/dL or higher compared to those with levels <3.5 g/dL, and in patients classified as ISS stage II-III compared to those with ISS stage I. Conditioning with ^{166}Ho-DOTMP was associated with a lower failure rate compared with melphalan alone, yet this effect did not reach statistical significance (Table 4). Because Beta 2 microglobulin is a part of the ISS, the independent effects of these 2 factors could not be evaluated. When potential confounding effects were evaluated in a bivariate model including conditioning regimen and ISS stage I results were consistent with univariate analysis indicating that the effects of these factors are independent. Similarly, results were consistent with univariate analysis when ISS stage I was substituted with elevated Beta 2 microglobulin level in the bivariate model (data not shown).

DISCUSSION

^{166}Ho-DOTMP is a beta-emitting radiophosphonate that localizes to areas of active bone turnover and can be a useful agent in the preparative regimens for ASCT in patients with MM. The results of a multicenter phase I/II trial have been previously reported [17]. The acute toxicity profile was no different from melphalan alone, and engraftment was prompt in most of the patients. However, the development of late renal dysfunction in 18% of all patients demonstrated that targeting a specific marrow dose without limiting the total amount of ^{166}Ho-DOTMP delivered would not be feasible. In the phase I/II trials of ^{166}Ho-DOTMP grade 3-4 renal toxicity was seen primarily in patients receiving >1200 mCi/m^2 of ^{166}Ho-DOTMP.

In the present study, we retrospectively analyzed the transplant outcomes of the 41 patients treated in a single center with a ^{166}Ho-DOTMP-containing regimen between January 1998 and December 2001 (groups A and B), and compared them with the transplant outcomes of 63 patients treated with high-dose melphalan followed by ASCT in the same time frame (group C). To evaluate the effect of ^{166}Ho-DOTMP dosing on outcomes we analyzed separately patients who received <2400 mCi of ^{166}Ho-DOTMP (group A) and those who received 2400 mCi or more (group B).

Patients in group A had a similar NRM rate as patients receiving melphalan alone during the same time period (5% and 3.2%, respectively). Patients in group A also had a trend towards a high rate of conversion to CR and a longer EFS (median 30 months versus 19 months) and OS (61% versus 42%

Table 3. *Prognostic Factors for Overall Survival Groups A and C Only*

Variable	N	Univariate HR	95% CI	Multivariate HR	95% CI	P
Conditioning Regimen						
Group C	63	ref				
Group A	21	0.63	0.3-1.5	0.7	0.3-1.6	.4
Gender						
Female	33	ref				
Male	51	0.7	0.3-1.4			
Age						
≤50	23	ref				
51-55	19	0.8	0.3-2.2			
56-60	26	1.5	0.7-3.5			
>60	16	0.6	0.2-1.9			
Disease status prior to SCT						
1ry refractory	24	ref				
1st remission	55	1.1	0.5-2.5			
Complete remission	5	1.2	0.25-5.4			
Beta 2 microglobulin at SCT						
<3.5	54					
≥3.5	25	ref				
Unknown	5	2.5	1.2-4.7$_{P = .02}$			
Albumin at SCT						
<3.5	23	ref				
≥3.5	61	0.6	0.3-1.05$_{P = .07}$			
International staging system at SCT						
I	43	ref				
II	24	2.0	0.9-4.3$_{P = .08}$			
III	11	2.1	0.8-5.6$_{P = .12}$			
Unknown	6					
I versus II-III		0.6	0.2-0.98$_{P = .045}$	0.5	0.2-1.03	.06

CI indicates confidence interval; HR, hazard ratio; SCT, stem cell transplant.

Table 4. *Prognostic Factors for Event-Free Survival Groups A and C Only*

Variable	N	Univariate HR	95% CI	Multivariate HR	95% CI	P
Conditioning regimen						
Group C	63	ref				
Group A	21	0.6	0.3-1.1 $_{P = .1}$	0.6	0.3-1.2	.2
Gender						
Female	33	ref				
Male	51	1.3	0.8-2.2			
Age						
≤50	23	ref				
51-55	19	0.8	0.4-1.6			
56-60	26	1.2	0.6-2.2			
>60	16	0.7	0.3-1.6			
Disease status prior to SCT						
1 ry Refractory	24	ref				
1st Remission	55	1.2	0.7-2.2			
Complete remission	5	0.5	0.1-2.2			
Beta 2 microglobulin at SCT						
<3.5	54	ref				
≥3.5	25	2.2	1.4-4.5 $_{P = .003}$			
Unknown	5					
Albumin at SCT						
<3.5	23	ref				
≥3.5	61	0.6	0.3-1.05 $_{P = .07}$			
International staging system at SCT						
I	43	ref				
II	24	2.2	1.25-3.97 $_{P = .006}$			
III	11	2.1	1.02-4.5 $_{P = .045}$			
Unknown	6	0.6				
I versus II-III			0.3-1.05 $_{P = .05}$	0.5	0.3-0.9	.01

CI indicates confidence interval; HR, hazard ratio; SCT, stem cell transplant.

at 5 years) than patients in group C, suggesting that the doses of 2400 mCi or less are the most appropriate to exploit the therapeutic effects of this agent. On multivariate analysis only, the ISS score at the time of SCT was associated with a significant improved survival. This observation is interesting, because the ISS score was developed as a prognostic factor for patients with newly diagnosed myeloma, and the prognostic value of pretransplant ISS has not been established. We were unable to assess the impact of ISS at the time of diagnosis because of the large proportion of patients in whom Beta 2 microglobulin at the time of diagnosis was unavailable.

There is a growing experience with targeted skeletal radiotherapy in human malignancies. Apart from ^{166}Ho-DOTMP, ^{153}Sm-EDTMP is currently being tested in patients with MM in combination with high-dose melphalan. The toxicity profile of red marrow doses up to 40 Gy given in 18 patients was excellent after a median follow-up of 31 months [24].

These results, although not statistically significant because of the low patient number and the nonuniform treatment strategy, provide encouraging information and support further exploration of targeted skeletal radiotherapy as a component of the preparative regimens of ASCT.

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