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RESEARCH

Total marrow irradiation as part of autologous stem cell transplantation for patients with multiple myeloma

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Abstract

The efficacy and safety of total marrow irradiation (TMI) plus a reduced dose of melphalan as autologous stem cell transplantation (ASCT) preconditioning for multiple myeloma (MM) patients were evaluated. The 11 patients with MM had a median age of 57 (range: 46–75) years; six of them were at standard risk and five of them were at high risk based on the Mayo Stratification of Myeloma and Risk-adapted Therapy (mSMART) standard risk factors. Before ASCT, three patients achieved stringent complete response (sCR), two patients achieved complete remission (CR), and the rest of the patients had either partial response (PR) or progressive disease. Most of the 11 patients were pretreated with melphalan 120–140 mg/m^2 and TMI 12 Gy. The intravenous infusion median mononuclear cell count (MNC) was 8.13 (4.16–11.84) × 10^8/kg, and the median CD34$^+$ count was 4.74 (2.51–21.98) × 10^6/kg. The minimal residual disease (MRD) in the grafts as determined by flow cytometry (FCM) and fluorescence in situ hybridization (FISH) were negative in 10 patients but positive in the progressive patient. All patients stopped maintenance therapy after transplantation, and further observation focused on the efficacy and tolerability of the transplantation. The neutropenic and thrombocytopenia durations were 11 (7–28) and 14 (8–70) days, respectively. The primary acute non-hematological toxicities were mild oral and gastrointestinal mucositis; there were no transplant-related deaths or serious complications. Of the eight patients who did not achieve sCR before transplantation, seven converted to sCR and one converted to VGPR after transplantation. The median follow-up period was 24 (10–57.5) months. Only one patient relapsed, and the progression-free survival (PFS) was 90.9%, while the overall survival (OS) was 100%. Our preliminary results suggest that melphalan 120–140 mg/m^2 plus TMI 12 Gy/6f as a conditioning regimen is safe and efficient for patients with MM.

Keywords Total marrow irradiation · Melphalan · Autologous stem cell transplantation · Multiple myeloma

Introduction

Although the efficacy of proteasome inhibitors, lenalidomide, and anti-CD38 monoclonal antibody in treating multiple myeloma (MM) has greatly improved in recent years, autologous stem cell transplantation (ASCT) is still the preferred treatment for patients with MM who are ≤65 years old. Among the many preconditioning regimens that have been used for ASCT, a high dose of melphalan at 200 mg/m^2 (HDM200) has been recommended by various guidelines as the standard preconditioning regimen for MM patients [1]. The preconditioning regimen consisting of total body irradiation (TBI) was abandoned because of its higher incidence of adverse reactions and because its overall survival (OS) was not superior to that of HDM200 [2]. MM is more common among elderly individuals, who are usually complicated by a variety of underlying diseases, which limit the doses of preconditioning drugs and may be important factors affecting the long-term effect of ASCT. The application of total marrow irradiation (TMI) can significantly reduce the irradiation dose of extramedullary tissues and organs,

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with the effect of reducing the side effects and killing more myeloma cells [3]. However, there have been only a few reports on the use of TMI for MM preconditioning [4]. In our study, we discuss the efficacy and safety of this regimen, as well as the long-term follow-up results, in 11 patients who completed ASCT after preconditioning with melphalan 120–140 mg/m^2 plus TMI 12 Gy and who did not undergo maintenance therapy.

Patients and methods

Patients

We enrolled 11 symptomatic patients with MM who underwent ASCT at Dongguan Kanghua Hospital (between July 2019 and December 2023). The eligibility criteria included age ≤ 75 years and symptomatic MM. Patients were excluded if they had the following: (1) previous radiotherapy; (2) severe abnormalities of cardiac, pulmonary, or hepatic function; or (3) serum creatinine levels > 2 mg/dL. All patients gave informed consent, and the study was approved by the institutional ethics committee of the Dongguan Kanghua Hospital. The characteristics of the 11 patients are presented in Table 1. The median age was 57 (range: 46–75) years. Based on the myeloma immune classification, there were two patients with IgA-k, three patients with IgA-λ, four patients with IgG-k, one patient with IgG-λ, and one patient with light chain k. Six of these patients were at standard risk and five were at high risk based on the Mayo Stratification of Myeloma and Risk-adapted Therapy (mSMART) standard risk factors. All patients received 3–8 cycles of treatment before ASCT, but no patient had received prior radiotherapy. Three patients achieved stringent complete response (sCR), two patients achieved complete response (CR), two patients achieved very good partial response (VGPR), and two patients achieved partial response (PR) before ASCT; one patient had stable disease (SD), and one patient had progressive disease (PD). The minimal residual disease (MRD), as determined using flow cytometry (FCM), in the 11 patients are presented in Table 1.

Stem cell mobilization and collection

The patients received at least three cycles of treatment before stem cell mobilization. Six patients received one course of cyclophosphamide 1.0–1.2 g/m^2 d1–3 with granulocyte colony-stimulating factor (G-CSF) mobilization, and four of them received subcutaneous injections of 20 mg of prexafol 11 h before stem cell collection. Another five patients received one course of G-CSF plus prexafol to mobilize their stem cells. The stem cells were collected on the fifth day after G-CSF using a Fresenius blood cell separator. The median count of mononuclear cells (MNCs) in the stem cell products was 15.62×10^8/kg (range $4.54–20.02 \times 10^8$/kg), and the median count of CD34$^+$ cells was 8.54×10^6/

Table 1 Clinical data of the 11 patients before ASCT

No.	Sex	Age	Immune type	Stage			high risk factor	Before ASCT			
				ISS	R-ISS	mSMART		regimen	course	MM state	FCM-MRD(%)
1	Man	46	IgG-κ	II	II	Standard risk	No	PAD	4	CR	0.06
2	Man	54	IgA-λ	III	III	High risk	No	PAD	5	sCR	0
3	Female	62	IgG-λ	III	III	High risk	t(4;14), 1q21 amplification	VCD	8	sCR	0
4	Man	66	IgA-κ	I	I	Standard risk	No	VRD	3	sCR	0
5	Man	53	IgA-κ	III	III	High risk	t(4;14)	VCDx1 ICDx2 ICRDx5	8	VGPR	0.1
6	Man	65	IgA-λ	I	I	Standard risk	No	ICD	3	SD	1.8
7	Man	57	IgG-κ	II	II	Standard risk	No	VRDx4 VCDx1	5	PR	0
8	Man	75	IgA-λ	II	II	Standard risk	No	VCDx1 VCRDx7	8	PD	2.8
9	Female	63	IgG-κ	III	II	Standard risk	No	ICDx4 ICDRx2 ICDBx2	8	PR	0.06
10	Man	56	κ	III	III	High risk	No	ICD	3	CR	0
11	Man	51	IgG-κ	III	III	High risk	t(11;14),t(4;14), t(14;16),t(14;20)	ICDx2 KCDx2	4	VGPR	0

Note: PAD: bortezomib + liposomal doxorubicin + dexamethasone; VCD: bortezomib + cyclophosphamide + dexamethasone; VRD: bortezomib + lenalidomide + dexamethasone; VCDR: bortezomib + cyclophosphamide + dexamethasone + lenalidomide; ICD: isazzomib + cyclophosphamide + dexamethasone; ICDR: isazzomib + cyclophosphamide + lenalidomide + dexamethasone; ICDB: isazzomib + cyclophosphamide + pomadomide + dexamethasone; KCD: carfilzomib + cyclophosphamide + dexamethasone

kg (range 2.47–23.99 × 10^6/kg). The cells were frozen in a stem cell freezer prior to ACST. Three-laser 10-color FCM and fluorescence in situ hybridization (FISH) were used to detect MRD in the stem cell products; further, 10 patients were negative for MRD, but one patient was positive, with 16% P53 deletion detected by FISH and 0.0499% clonal plasma cells detected by FCM.

Pretreatment scheme

Two weeks to a month after peripheral blood stem cell (PBSC) collection, the patients were evaluated, and no contraindications were noted in any of them. The patients then received TMI and melphalan for preconditioning. Ten patients received TMI 12 Gy/6f, and this was reduced to 10 Gy/5f for the 75-year-old patient. The pretreatment scheme was TMI 200 cGy b.i.d on days −5 to −3, melphalan 120–140 mg/m^2 divided over 2 d (days −2 and −1). Nine patients received melphalan 140 mg/m^2, one patient received melphalan 130 mg/m^2, and one patient received melphalan 120 mg/m^2, all administered through intravenous infusion over the course of 30 min for each dose.

The volumetric rotational intensity modulated radiotherapy technique was used, in which the skeleton of the whole body was delineated as the planning target volume (PTV) for the target area, with 0.3 cm placed outside the skull and 0.5 cm outside the bones of the rest of the chest, abdomen, and four limbs. The prescription dose was 200 cGy twice per day for a total dose of 1000–1200 cGy to the PTV over an interval of more than 6 h, and the target dose was 100%. The irradiation doses of the extramedullary organs involved in irradiation were 7.2 ± 0.4 Gy for the left lung, 7.3 ± 0.4 Gy for the right lung, 7.0 ± 0.6 Gy for the left kidney, and 6.9 ± 0.4 Gy for the right kidney. The maximum mean irradiation dose for the left lens was 3.8 ± 1.2 Gy, that for the right lens was 3.9 ± 1.2 Gy, that for the liver was 7.8 ± 0.4 Gy, and that for the heart was 7.0 ± 0.4 Gy. The other normal organ limits were within the range of standard requirements, and all patients passed the dose verification.

Four of the eleven patients underwent a second transplantation 3–6 months after the first transplantation as consolidation therapy. The preconditioning regimen for the second transplantation was melphalan alone at 140 mg/m^2. None of the 11 patients received maintenance therapy after ASCT.

Stem cell transfusion and complication prevention

PBSC transplantation was carried out on day 0. The median MNC count was 8.13 (4.16–11.84) × 10^8/kg, and the median $CD34^+$ cell count was 4.74 (2.51–21.98) × 10^6/kg. G-CSF was recommended from day 2 after transplantation until granulocyte recovery. During the myelosuppression period, blood transfusion was performed if necessary, and symptomatic supportive treatments such as antibiotics were given when the patients developed agranulocytosis with fever. In addition, patients with diarrhea in the extreme stage of acute radiation sickness received budesonide capsules 3 mg t.i.d orally before the elimination of diarrhea.

Follow-up and response criteria

The granulocyte recovery time was from day + 1 to when the peripheral blood neutrophil count was > 0.5 × 10^9/L for three consecutive tests, and the megakaryocyte recovery time was from day + 1 to when the peripheral blood platelet count was > 20 × 10^9/L for three consecutive tests without platelet transfusion. Routine biochemical project tests were performed twice a week before hematopoietic recovery, and abnormal findings were reviewed at the appropriate time. After hematopoietic recovery, serum protein electrophoresis, as well as blood and urine immunofixation electrophoresis, were performed every three months until sCR was achieved; those who achieved sCR were tested every three months. Bone marrow cytology and FCM-based MRD were checked periodically post-ASCT. Toxicity of treatment was scored according to the Common Terminology Criteria for Adverse Events v5.0. According to the efficacy criteria of the International Myeloma Working Group 2016, the efficacy of myeloma can be divided into sCR, CR, VGPR, PR, SD, and PD. sCR was defined as meeting the criteria for CR, the serum free light chain ratio was normal, and there were no clonal plasma cells in the bone marrow. CR was defined as the absence of serum and urinary M-protein and no more than 5% plasma cells in the bone marrow. VGPR was defined as 90% or greater decrease in blood M-protein levels and M-protein levels in the urine < 100 mg/24 h. PR was defined as 50% or greater decrease in blood M-protein levels and M-protein levels in the urine < 200 mg/24 h, or the reduction was ≥ 90%. SD was defined as not conforming to the criteria of CR, VGPR, PR, or PD, and there was no new osteopathy or progression of an existing osteopathy. PD was defined as a > 25% increase in M protein levels, a > 25% increase in bone marrow plasma cells, or new bone lesions. OS was defined as the time from pretreatment until death from any cause or the last follow-up, and progression-free survival (PFS) was defined as the time from hematopoietic recovery until disease progression. The last follow-up was on May 15, 2024.

Statistical analysis

Descriptive statistical analyses were applied for patient and disease characteristics, treatment features, and toxicity.

Results

Hematopoietic recovery

Hematopoietic recovery was successful in all patients. The median time of granulocyte hematopoietic recovery was 11 (7–28) days, and the median time of megakaryocyte recovery was 14 (8–70) days. With the exception of a 75-year-old patient who underwent ASCT at the stage of disease progression, leukocyte and platelet recovery took 28 days and 70 days, respectively, and hematopoietic recovery was completed in all patients within 2 weeks. Two of the four patients who received secondary transplantation had hematopoietic recovery within 2 weeks, and the other two patients had hematopoietic recovery within 3 weeks.

Response to ASCT

All patients could be evaluated for efficacy. Table 2 shows the patient responses to transplantation. After transplantation, 10 patients achieved sCR, and one patient changed from PR to VGPR. All patients achieved negative FCM-MRD results (Table 2). The sCR rate was 90.9%, and the rate of sCR plus VGPR was 100%.

The median follow-up time was 24 (10–57.5) months. The OS was 100% and PFS rate was 90.9%. Only one patient progressed and none of the patients died. Nine patients had sustained sCR, with the first patient to achieve it sustaining it for 57 months. The patient who changed from PR to VGPR after transplantation achieved a continuous decline in M protein levels and was without recurrence during the 19.9 months of follow-up. The 75-year-old patient in whom the MM progressed with P53 deletion and whose graft was positive for MRD achieved sCR at 3 months after transplantation, and both the bone marrow MRD and P53 deletion were negative for at least 18.5 months until the last follow-up time. Figure 1 shows the disease state of the 11 patients after ASCT. The zero time indicates the beginning of the pretreatment.

Non-hematological toxicity

The main acute non-hematological toxicity from the TMI combined with melphalan 120–140 mg/m^2 took the form of oral mucositis and nausea, vomiting, and diarrhea, all of which were of grade I to III. Only one patient showed grade IV asymptomatic elevation of blood amylase. There were no transplant-related deaths, and the 75-year-old patient tolerated the treatment well. All of the results are shown in Table 2. There were no significant differences in terms of the side effects of HDM200 compared to previous reports in the published literature, and there were no secondary malignancies or other chronic toxicities during follow-up.

Discussion

In this study, we analyzed the efficacy and safety of TMI plus reduced melphalan as a preconditioning regimen for ASCT. The results showed that 10 patients achieved sCR, while one patient changed from PR to VGPR after transplantation. The sCR rate was 90.9%, the rate of sCR plus VGPR was 100%, and the depth of efficacy was significantly better than that of HDM200 [2, 5]. In addition, the hematopoietic recovery time and adverse reactions were similar to those reported for HDM200 in the literature [5]. The primary acute non-hematological toxicities were mild oral and gastrointestinal mucositis, which were cured within one week after symptomatic treatment; moreover, there were no transplant-related deaths or serious complications. This was similar to the toxicity of HDM200, but less than that of TBI reported in the literature [5]. In terms of long-term (i.e., chronic) adverse reactions, it has been reported that the incidence of genital tumors in patients who received TMI is significantly lower than that in patients who received TBI [6]. In our study, no patient developed a second tumor during follow-up. Our preliminary results suggest that TMI may be safer and more effective, and it is worth increasing the number of cases for further examination.

A prospective study of sequential ASCT followed by therapy with first- or second-generation drugs revealed that MM patients can benefit from ASCT [7]. ASCT is an important treatment for patients with unfavorable risk MM, even if induction therapy includes CD38 monoclonal antibody [8]. The pretreatment regimen is closely related to the occurrence of transplant-related adverse reactions, the reconstruction of immune function, and the PFS of patients with MM. HDM200 is recommended as the standard preconditioning regimen by current guidelines because cyclophosphamide plus etoposide and busulfan (CVB) or busulfan plus cyclophosphamide (BUCY) are not better than HDM200 for patients with MM [1, 9]. However, the rate of MM progression after ASCT without maintenance therapy remains high. The combination of radiotherapy with chemotherapy may improve the clearance efficiency of MRD and increase PFS. Thus, it is of great significance to explore safe and effective combinations radiotherapy with chemotherapy.

In a multicenter randomized clinical study from France, 282 patients with MM aged 60–65 years from 42 centers were randomized into 140 patients treated with TBI 8 Gy plus melphalan 140 mg/m^2 and 142 patients treated with HDM200. The results showed that there was no significant difference in efficacy between the two groups after

Table 2 Results of the 11 patients after ASCT

No.	MM state	FCM-MRD	Time (month)			Acute or subacute adverse reactions and severity grading						
			Follow up	PFS	OS	Granulocyte recovery (days)	Megakaryon recovery (days)	Infection	Oral mucositis	Nausea and vomiting	Diarrhea	Serum amylase increased
1	sCR	0	57.5	57	57.5	7	8	Septicemia	I	No	I	No
2	sCR	0	44.5	44	44.5	10	11	Agranulocytosis with fever	I	IV	III	IV
3	sCR relapse[#]	0	40	36	40	11	11	No	II	II	III	II
4	sCR	0	34.5	34	34.5	10	14	Agranulocytosis with fever	I	III	III	I
5	sCR	0	24.5	24	24.5	10	12	No	I	No	II	No
6	sCR	0	24	23.5	24	11	21	Agranulocytosis with fever	I	No	III	No
7	VGPR	0	19.9	19.3	19.9	13	18	No	II	No	II	No
8	sCR	0	18.7	17.6	18.7	28	70	Agranulocytosis with fever	I	No	III	I
9	sCR	0	18.5	17.8	18.5	14	22	Septicemia	I	I	II	No
10	sCR	0	12.1	11.6	12.1	11	14	No	No	I	I	No
11	sCR	0	10.0	9.5	10.0	12	13	No	No	No	I	No

Note: "#" indicates that patient 3 achieved sCR for 36 months, but she recurred at the 37th month after transplantation

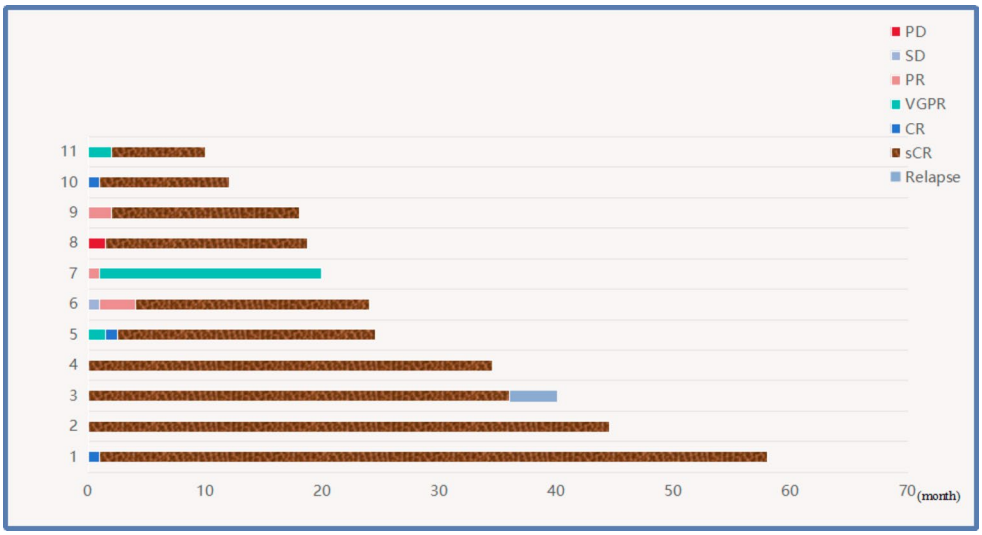

Fig. 1 Efficacy evaluation and follow-up of the 11 patients after ASCT ("0" represents the beginning of the pretreatment. The ordinate is the number of cases, and the abscissa is the follow-up time (months). Different colors represent different disease states

transplantation, but the patients treated with TBI combined with melphalan had poorer tolerance and higher transplant-related mortality than those treated with HDM200 [2]. TBI inevitably exposes extramedullary tissues to high-dose radiation due to the lack of targeting, resulting in more transplant-related toxicity. However, MM often occurs in elderly patients, for whom TBI is not suitable due to their physical characteristics. The application of radiological techniques targeting the bone marrow or tumor lesions may decrease the adverse effects of TBI. Studies have shown that, in animal models, spiral tomography can reasonably allocate the radiation dose to the bone marrow and local tumor lesions, thereby reducing exposure to high radiation doses in important organs or tissues [10]. When the radiation dose of TMI was increased to 20 Gy, the exposure dose of the normal tissue and organs was significantly lower than that of TBI 12 Gy [3]. Regarding the incidence of radiation-related tumors, the risk of genital tumors in the TMI 20 Gy treatment was significantly lower than that in the TBI 12 Gy treatment [6]. Scholars have compared the advantages and disadvantages of TMI and TBI; for example, Mümtaz Köksal confirmed that implementing effective TMI protocols achieved significant dose reduction in organs at risk while still achieving the prescribed dose in the target areas [11]. Pei-Wei Shueng and Shih-Chiang Lin have shown that preconditioning with TMI 12 Gy is feasible for patients with acute leukemia or MM [12–14]. In our study, the TMI dose was based on successful doses reported in the literature [4, 12, 14], and the toxicity in the 10 patients pretreated with TMI 12 Gy plus a reduced dose of melphalan was well tolerated.

Many studies have shown that maintenance therapy following ASCT is more beneficial than non-maintenance therapy for treating MM, as maintenance therapy can further improve the efficacy and PFS [15, 16]; thus, maintenance therapy is recommended by the international authoritative guidelines for the diagnosis and treatment of MM. However, there is no clear end point for maintenance therapy. Its endpoint usually set as disease progression, patient refusal of treatment, or intolerance of treatment. Moreover, long-term maintenance therapy brings significant adverse reactions and increased medical costs. Thus, whether and how maintenance therapy should be used requires further investigation. Giebel et al. reported a PFS of 55% and OS of 74% after 5 years in ASCT patients with MM pretreated through TMI and without maintenance therapy after ASCT [4]. Another study showed that among 186 patients who achieved MRD negativity at least once during maintenance therapy, 24 patients stopped treatment while the remaining 162 patients continued maintenance therapy, and there was no significant difference in their PFS (120 vs. 82 months) [17], suggesting that MRD-negative patients did not significantly benefit from maintenance therapy. In our study, none of the 11 patients received maintenance therapy after transplantation, and only one patient relapsed at a median follow-up of 24 months. Moreover, the 2-year OS rate was 100% and the 2-year PFS rate was 90.9%, which are significantly higher than those reported in the literature [18]. These results indicate that maintenance therapy after ASCT is not necessary, and its precise implementation needs further investigation. Negative MRD may be one of the primary factors used to determine when to stop maintenance therapy.

In sum, our preliminary results suggest that TMI 12 Gy plus melphalan 120–140 mg/m^2 is safe and effective, and the PFS without maintenance therapy is very high at 2 years of follow-up; this high PFS may be related to negative MRD. However, due to the small sample size, further studies should be carried out to increase the number of cases.

Conclusion

In summary, total marrow irradiation plus reduced melphalan is an effective and safe conditioning regimen for patients with MM. The results of this study are worthy of further research to increase the number of cases.

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Author contributions Q.Z. performed clinical observation, collected and analyzed the data, wrote the manuscript. H.C.,X.W.,S.H.,M.W.,D.Y. and J.L.performed clinical observation, collected and described the clinical material.X.L. and Y.X. designed and developed the whole bone marrow irradiation program.J.Y. performed laboratory research.Y.W. diagnosed and treated partial cases before transplantation.H.H. was responsible for patient care.F.M. designed the study, guided the clinical treatment, monitored the project progress, reviewed the data and critically reviewed and edited the manuscript. All listed authors have read and approved the final submitted version.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval We enrolled 11 symptomatic patients with MM who underwent ASCT at Dongguan Kanghua Hospital (between July 2019 and December 2023). All patients gave informed consent, and the study was approved by the by the institutional ethics committee of the Dongguan Kanghua Hospital.

Consent to participate All patients and authors agreed to participate in the study.

Consent for publication All the authors agreed to publish the study.

Competing interests The authors declare no competing interests.

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