SY Ma 馬承恩
AKW Lie 李國維
WY Au 區永仁
CS Chim 詹楚生
YL Kwong 鄺沃林
R Liang 梁憲孫

Non-myeloablative allogeneic peripheral stem cell transplantation for multiple myeloma

以非清髓異體外周幹細胞移植治療多發性骨髓瘤

Objective. To present an institution's 2-year experience of non-myeloablative allogeneic stem cell transplantation among Chinese patients.
Design. Retrospective study.
Setting. Bone marrow transplantation unit at a university hospital, Hong Kong.
Patients. Ten patients with multiple myeloma who received non-myeloablative allogeneic stem cell transplantation between March 2000 and October 2002.
Intervention. Fludarabine (90 mg/m^2) and total body irradiation (300 cGy) were given as conditioning regimens, followed by non-myeloablative allogeneic stem cell transplantation.
Main outcome measures. Engraftment, regimen-related toxicity, treatment-related mortality (in the first 100 days), incidence of graft-versus-host disease, chimerism, disease response, and survival rate.
Results. All 10 patients had active disease before transplantation. The donors were eight human leukocyte antigen–matched siblings, a mismatched sibling, and a matched daughter. Satisfactory engraftment before day 21 was achieved without early treatment-related mortality. Five patients developed full donor chimerism by day 28 and three other patients had 100% donor chimerism by day 100. Acute graft-versus-host disease developed in six patients (five with grade III and one with grade IV disease), and chronic graft-versus-host disease developed in eight patients (four with extensive disease). Complete remission and partial response were achieved in three and four patients, respectively. Three patients did not respond to treatment, and one case of relapse was observed. Only one patient, who had shown a partial response, received donor lymphocyte infusion; seven patients received thalidomide for graft-versus-host disease with or without graft-versus-myeloma effect. All patients were alive after a median follow-up of 1 year.
Conclusion. Non-myeloablative allogeneic stem cell transplantation for multiple myeloma is effective, has low toxicity, and results in low treatment-related mortality. Studies of more cases with longer follow-up durations are required.

目的：報告一所大學醫院在兩年期間，為華裔病者進行非清髓異體外周幹細胞移植的經驗。
設計：回顧研究。
安排：大學教學醫院骨髓移植部門，香港。
參與者：2000 年 3 月至 2002 年 10 月期間，10 名患上多發性骨髓瘤的病者接受非清髓異體外周幹細胞移植手術。
療法：以 fludarabine（90 mg/m^2）及全身放射（300 cGy）作為預處理，隨後進行非清髓異體外周幹細胞移植手術。
主要結果測量：成功植入骨髓、與治療有關的中毒、首100天內與療法有關的死亡率、移植物抗宿主疾病、嵌合、症狀反應及存活率。
結果：10位患者在移植前病情嚴重。幹細胞供者分別為8名人類白血球抗原相合的親屬、1名抗原不相合的親屬、以及1名抗原相合的女兒。術後第1至20天，移植效果理想，並無出現與療法有關的早期死亡。至第 28 天，有 5 位患者達至完全供體嵌合；另有3位患者在100天內達至完全供體嵌合。6名患者出現急性移植物抗宿主疾病（5 人屬第三級病症，1 人屬第四級病症），8 人出現慢性移植物抗宿主病（其中 4 人為晚期病症）。分別有 3 位及 4 位患者的症狀得到完全或局部緩解。其中 3 人對治療沒有反應；1 人出現復發。只有 1 位患者接受供體白血球輸注；他

Key words:
Multiple myeloma;
Myeloablative agents;
Transplantation

關鍵詞：
多發性骨髓瘤；
清髓劑；
移植

Hong Kong Med J 2004;10:77-83

Division of Haematology and Oncology, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong
SY Ma, MB, BS, MRCP
AKW Lie, FRCP, FHKAM (Medicine)
WY Au, MRCP, FHKAM (Medicine)
CS Chim, MD, FHKAM (Medicine)
YL Kwong, MD, FRCP
R Liang, MD, FRCP

Correspondence to: Prof R Liang (e-mail: rliang@hkucc.hku.hk)

的症狀得到局部緩解。7人接受thalidomide治療，以緩解移植物抗宿主症狀，當中部分出現移植物抗骨髓瘤宿主情況。中位數為1年的隨訪期屆滿後，所有患者仍然生存。

結論：非清髓異體外周幹細胞移植是治療多發性骨髓瘤一種有效的療法，其毒性低，引致與療法有關的死亡率亦偏低。但仍需要對更多病例進行研究，相應的隨訪期亦需要延長。

Introduction

Multiple myeloma is a malignant disorder of plasma cells. The disease is common in the elderly population; the median age at diagnosis is 65 years and the median survival time associated with conventional therapy is 3 years or less.[1] Multiple myeloma is incurable, however, and the complete remission rate and 10-year survival are less than 5%.[2] Autologous bone marrow transplantation (ABMT) has been used increasingly during the past 15 years and achieves a treatment-related mortality of less than 5% and a durable complete remission rate of 30% to 50% among newly diagnosed patients.[3] Two prospective randomised controlled trials and three other studies with historical comparisons have shown that ABMT is superior to conventional chemotherapy in terms of complete remission rate and event-free survival. However, the better overall survival attributed to ABMT was not substantiated in all studies and, more importantly, the survival curve did not reach a plateau, implying that this modality may not be curative and that factors such as conditioning regimen and optimal timing of ABMT still need to be improved.[4-7]

The role of allogeneic stem cell transplantation (allo-SCT) remains controversial in the management of multiple myeloma.[8,9] The European Group for Blood and Marrow Transplantation has shown no overall survival benefit of allo-SCT over ABMT,[10] because the treatment-related mortality after allo-SCT in the first 100 days is as high as 30% to 50%—mostly as a result of the old age of the patients, intensive chemotherapy before transplantation, and co-morbidity.[11,12] Still, about 40% of patients with complete remission can remain disease-free for 6 years and longer.[10,12] The graft-versus-myeloma (GVM) effect probably makes allo-SCT the only curative therapy for multiple myeloma.[10,13-15] Furthermore, donor lymphocyte infusion for relapse after allo-SCT gives satisfactory results.[16,17] The benefit of allo-SCT, however, is hampered by the high incidence of graft-versus-host disease (GVHD).[16,18]

In the past 5 years, the use of non-myeloablative conditioning regimens followed by stem cell infusion has been shown to achieve stable engraftment in various haematological malignancies.[19-24] Badros et al[25,26] found that non-myeloablative conditioning regimens based on melphalan 100 mg/m^2 in heavily pre-treated high-risk patients with multiple myeloma were well-tolerated; the protocol led to a lower treatment-related mortality and satisfactory donor engraftment. However, relevant data have not yet been documented for Chinese patients. In this article, we present our experience of non-myeloablative allo-SCT with fludarabine and total body irradiation as the conditioning regimen among 10 Chinese patients.

Patients and methods

Study design

From March 2000 to October 2002, 10 Chinese patients with multiple myeloma underwent non-myeloablative peripheral blood stem cell (PBSC) transplantation in the Bone Marrow Transplantation Unit of the Queen Mary Hospital. All patients had not achieved a complete response after chemotherapy, but suitable human leukocyte antigen (HLA)–matched donors were available. Written consent was obtained from both donors and recipients. The conditioning regimens consisted of intravenous fludarabine (30 mg/m^2) from day 5 to day 3 and total body irradiation (150 cGy) on days 2 and 1.

Prophylaxis for GVHD consisted of oral mycophenolate mofetil (15 mg/kg) twice daily from day 0 to 28 and intravenous cyclosporin, starting at a dosage of 1.2 mg·kg^{-1}·d^{-1} on day 1 (adjusted to a target serum level concentration of 250-300 ng/μL). Treatment was switched to oral cyclosporin if the drug was tolerated. Methotrexate was not included in the GVHD prophylaxis regimen. Cyclosporin was tapered gradually after day 60 in the absence of GVHD.

Bone marrow examination, serum immunoglobulin electrophoresis, and immunofixation were performed on day 28 and repeated at 3, 6, 12, 18, and 24 months to assess the disease status. Patients with persistent, progressive, or relapsed disease had immunosuppression discontinued in the absence of GVHD. If there was evidence of disease progression, donor lymphocyte infusion with or without oral thalidomide starting at 100 mg/d were administered.

Antimicrobial prophylaxis during the transplant period consisted of oral acyclovir 200 mg three times daily from day 0 to day 30 and oral fluconazole 200 mg/d and oral ciprofloxacin 500 mg two times daily from day 6 to day 30. Pentamidine inhalation 300 mg once every 3 weeks was also given and then switched to oral co-trimoxazole 960 mg two times per week if the neutrophil count recovered within 1 year. Polymerase chain reaction (PCR) analysis was used to check for cytomegalovirus (CMV) weekly in the first 100 days and then monthly until 1 year. Patients who were CMV-positive were tested for CMV pp65 antigenaemia and treated with ganciclovir (5 mg/kg) three times per week. In refractory cases, foscarnet (60 mg·kg^{-1}·d^{-1}) was administered.

On days 0 and 1, patients received an allogeneic PBSC graft from their HLA-matched donor that had been activated with granulocyte colony-stimulating factor (G-CSF). Subcutaneous G-CSF 10 $\mu g \cdot kg^{-1} \cdot d^{-1}$ had been given to the donor for 4 days and leukopheresis (>15 L) was performed on the fourth and fifth day. The target stem cell count was more than 1 x 10^6 CD34-bearing cells per kg of the patient's weight. Stem cells were not manipulated and were cryopreserved.

Study end-point

Engraftment, regimen-related toxicity, treatment-related mortality (in the first 100 days), acute GVHD incidence, and chimerism were the primary end-points of this study. Secondary end-points included disease response, survival rate, and chronic GVHD incidence. Acute GVHD was assessed according to the scale suggested by Glucksberg et al,[27] and chronic GVHD was defined as GVHD that occurred after 100 days and was graded as none, limited, or extensive.[28] Other toxicities were assessed using the United States National Cancer Institute criteria. Engraftment was defined as a neutrophil count of more than 0.5 x 10^9 /L for 3 consecutive days and an untransfused platelet count exceeding 20 x 10^9 /L. The degree of donor-recipient chimerism was assessed by performing a PCR assay of the short tandem repeats in the relevant locus according to published methods.[29] Chimerism was assessed on days 28 and 100 and thereafter when clinically indicated. The presence of more than 5% donor or recipient cells in the sample was defined as mixed chimerism (the assay is sensitive to detect chimerism if more than 5% donor DNA is present).

Complete remission was assumed to have occurred when monoclonal paraprotein in the serum and urine was undetectable for a minimum of 6 weeks by serum immunoglobulin electrophoresis and immunofixation, and when the bone marrow aspirate contained less than 5% of plasma cells. Complete remission with only positive immunofixation was defined as near-complete remission. A partial response was defined as a reduction in disease burden by more than 50%. Relapse implied a recurrence of monoclonal protein or bone marrow plasmacytosis in patients who had achieved complete remission. A patient was assumed to show no response if there was no change in the disease status. Progression was when the disease progressed in a patient who had previously shown partial remission or no response.

Results

Baseline characteristics of the study patients are shown in Table 1. The median age of the 10 patients (six men and four women) with multiple myeloma who received non-myeloablative PBSC transplantation was 51 years (range, 42-62 years). All patients presented at disease stage III (Durie and Salmon) at diagnosis and had been treated with chemotherapy only. The median number of chemotherapy regimens was 6.5. Only one patient had previously received an ABMT. Five patients had shown a partial response and five patients no response after chemotherapy at the time of transplant. Eight patients received a graft from HLA-matched siblings, one received a graft from her HLA-matched daughter, and the remaining patient received a HLA class-II (DR) antigen-mismatched graft from his sibling.

Clinical response, engraftment, and chimerism

A median of 1.84 x 10^6 CD34-positive cells per kg (range, 0.85-3.74 x 10^6) and 7.51 x 10^6 colony-forming unit–granulocyte-monocyte per kg (range, 0.95-23.00 x 10^6) were given to the patients. The median day for the onset of neutropenia was day 6 (range, 4-9) and the median day of engraftment was day 19 (range, 11-23). No patient required platelet transfusion. The lowest platelet count was 29 x 10^9 /L, and three of the 10 patients had a lowest platelet count of more than 100 x 10^9 /L. Six patients required a transfusion of red blood cells (four required 2 units and two required 4 units) and three patients required G-CSF after transplantation. Three patients had major ABO incompatibilities and there was no delayed engraftment or increased requirement for red blood cell transfusion in the first 100 days among these three patients. On day 28, half of the 10 patients had full donor chimerism and three other patients had full chimerism on day 100. Hence, eight patients displayed full chimerism and two had mixed chimerism (of 60% and 96%) on day 100 (Table 2).

The best responses of the bone marrow plasma cell and serum paraprotein after bone marrow transplantation are shown in Table 3. Three patients showed a complete response with undetectable paraprotein at 6 months, but one of them had a relapse at 1 year. Four patients had a partial response at a median follow-up of 1 year, and two of them subsequently showed disease progression. No extramedullary disease was recorded. Three patients displayed no response, with a follow-up period of 1 year in one patient and 4 months for the remaining two patients. Seven of the 10 patients received thalidomide for either GVHD treatment or augmented GVM effect, because the drug has been shown to be effective in these situations.[30,31] Only one patient, who had shown a partial response to treatment, had donor lymphocyte infusion at 6 months of follow-up for disease progression; no extensive GVHD was observed in this patient after infusion.

Overall survival, toxicity, and mortality

During follow-up (range, 80-960 days; median, 400 days), there were no patient deaths. The major regimen-related toxicity was GVHD. Six patients had acute GVHD: five with grade III and one with grade IV. The latter patient had received an HLA-mismatched graft from her sibling and developed grade-IV GVHD with a clinical picture of toxic epidermal necrosis; she was treated with anti-thymocyte globulin, mycophenolate mofetil, cyclosporin, steroid, and thalidomide. The skin GVHD in this patient recovered but she subsequently developed extensive chronic GVHD

Table 1. Baseline characteristics of the 10 patients undergoing non-myeloablative peripheral blood stem cell transplantation

Patient No.	Age (years)/sex	Donor's age (years)/sex	Donor's relationship	Human leukocyte antigen matching	Paraprotein subtype	Stage at presentation*
1	52/M	46/M	Sibling	Full	G/Kappa	IIIA
2	56/M	56/F	Sibling	Full	A/Lambda	IIIB
3	50/M	50/M	Sibling	Full	G/Kappa	IIIA
4	42/M	37/M	Sibling	Full	A/Beta	IIIA
5	47/M	49/F	Sibling	Full	A/Lambda	IIIA
6	57/F	55/M	Sibling	Full	G/Lambda	IIIA
7	50/M	37/F	Sibling	Full	D/Lambda	IIIB
8	48/F	35/M	Sibling	Minor antigen mismatch	G/Kappa	IIIA
9	62/F	67/M	Sibling	Full	G/Kappa	IIIA
10	56/F	29/F	Daughter	Full	G/Lambda	IIIA

* Durie and Salmon staging
† Reference level, <1.5 μg/mL
‡ VAD vincristine/adriamycin/dexamethasone
§ VCMP vincristine/cyclophosphamide/melphalan/prednisolone
‖ MP melphalan/prednisolone

Table 2. Clinical course and outcome after stem cell transplantation

Patient No.	Duration of neutrophil engraftment (days)*	Duration of neutropenia (days)†	Red blood cell transfusion (units)	Granulocyte colony-stimulating factor used	Donor chimerism day 28/day 100 (%)
1	21	6	4	No	100/100
2	17	5	0	No	75/100
3	22	6	2	Yes	96/100
4	21	5	4	No	92/100
5	18	6	0	Yes	89/60
6	11	9	0	No	88/96
7	20	8	2	No	100/100
8	23	6	0	No	100/100
9	19	4	2	No	100/100
10	18	7	2	Yes	100/100

* No. of days to achieve an absolute neutrophil count of >0.5 x 10^9 /L
† Since first day when neutrophil count was <0.5 x 10^9 /L
‡ Numbers in parentheses indicate the grading of acute graft-versus-host disease
§ aGVHD acute graft-versus-host disease
‖ Treated with anti-thymocyte globulin, mycophenolate mofetil, cyclosporin, steroid, and thalidomide

Table 3. Paraprotein and bone marrow response

Patient No.	Bone marrow plasma cell level (%)		Serum paraprotein level (g/L)			
	Pre-transplantation	Post-transplantation*	Pre-transplantation	Post-transplantation*	Change†	Time to best response (months)
1	10	12	21	5.7	-72%	18
2	21	2	24	9	-62%	24
3	23	2	30.5	3.8	-87%	12
4	16	1	34	0	-100%	6
5	10	10	Trace‡	12	N/A‖	6
6	15	1	26	0	-100%	6
7	>50	2	Trace‡	0	N/A	3
8	10	1	14.4	7.6	-47%	3
9§	>50	>50	40	53.5	+33%	3
10§	38	28	51.2	36.4	-28%	3

* Values are at best response
† % change compared with pre-transplantation value
‡ Positive immunofixation only
§ Patients 9 and 10 had 4 months of follow-up only
‖ N/A not applicable

involving the liver and lung (bronchiolitis obliterans). Four patients had extensive chronic GVHD (two with complete remission and two with a partial response) and four had limited GVHD. In contrast, two of the three patients who showed no response had limited chronic GVHD only. The third patient who had displayed complete remission did not have chronic GVHD but relapsed subsequently. Five months after transplantation, one of the three patients with complete

β_2-microglobulin at presentation (μg/mL)[†]	Chemotherapy before transplantation	Transplantation of autologous bone marrow before stem cells	Months from last chemotherapy to transplantation	Status at transplantation	Major ABO mismatch (donor to recipient)
1.5	VAD[‡]x5, VCMP[§]x7, MP[‖]x3	No	6	Partial response	Yes (A to B)
2.8	MPx1, VADx2	No	2	Partial response	No (A to A)
-	MPx2, VADx3	No	3	No response	Yes (B to O)
3.0	MPx2, VADx5, VCMPx2	No	1	No response	No (A to A)
Not applicable	VADx6	No	3	Partial response	No (A to A)
3.2	MPx2, VADx5	No	1	Partial response	No (B to AB)
5.4	MPx7	No	12	No response	No (O to AB)
5.3	VADx4	Yes	6	Partial response	No (A to A)
5.6	VADx6	No	4	No response	Yes (B to A)
2.3	VADx7, VCMPx6	No	1	No response	No (A to A)

Acute graft-versus-host disease[‡]	Thalidomide used	Chronic graft-versus-host disease	Outcome
Liver (2)	Yes	Limited	Partial response at 18 months then disease progression; donor lymphocyte infusion at 6 months
Gut (2)	Yes	Extensive	Partial response at 6 months, then disease progression and brochiolitis obliterans
Skin (3), gut (3), mucositis	Yes	Limited	Partial response at 22 months
None	Yes	Extensive	Complete remission since 6 months
None	Yes	Limited	No response at 1 year
None	Yes	No	Complete remission at 6 months but relapse at 12 months
Skin (2), gut (2)	No	Extensive	Complete remission at 6 months; carcinoma of stomach at 5 months, managed by gastrectomy
Skin (4), liver (4)	Yes	Extensive	Partial response at 6 months, stage IV aGVHD[§] of skin and liver[‖], and toxic epidermal necrosis
None	No	Limited	No response at 4 months
Skin (2), gut (2)	No	Too early to tell	No response at 4 months

remission had carcinoma of the stomach, which was treated with gastrectomy (Table 2). No cases of severe septicaemia or fungal infection were documented. Seven patients had CMV reactivation that were detectable by PCR analysis and all of them and their donors were CMV antibody–positive. Four of these seven patients were treated with ganciclovir alone and three received both ganciclovir and foscarnet. None of the patients developed clinical CMV disease.

Discussion

Multiple myeloma is common in the elderly age-group and is considered incurable using chemotherapy alone. Although traditional allo-SCT can result in a 50% complete remission rate at 6 years, the unacceptably high early treatment-related mortality (30%-50%) makes its application very limited.[10-12] The emergence of non-myeloablative PBSC (known as mini-PBSC) transplantation offers new hope to patients with multiple myeloma, especially to those who may have co-morbidities and those who have been heavily treated with chemotherapy, thereby rendering them unsuitable for conventional allo-SCT. Some reports have shown that mini-PBSC for multiple myeloma can achieve satisfactory engraftment and much lower early treatment-related mortality.[25,26]

Half of the patients in our series achieved full donor chimerism before day 28, and three other patients had full donor chimerism by day 100; thus, 80% of patients developed full chimerism. Sequential donor lymphocyte infusion was omitted because of the high incidence of GVHD after infusion in this setting.[25,26] Only one of the patients received donor lymphocyte infusion at 6 months because of progressive disease. The overall incidence of acute GVHD (60%) is comparable to that associated with conventional allo-SCT. However, the fact that all acute GVHD cases were grade III or above is of great concern. Our short course of mycophenolate mofetil for GVHD prophylaxis (from day 0 to day 28 only) may be insufficient because of the more severe acute GVHD: extensive debilitating chronic GVHD developed in four patients. Yet, the follow-up duration is relatively short and the true

chronic GVHD incidence is expected to be higher. The phenomenon of delayed engraftment resulting from ABO-incompatibility is still controversial.[32,33] In our study, the three ABO-incompatible recipients did not experience a delay in engraftment. A decreased requirement for transfusion was reported in patients receiving non-myeloablative transplantation when compared with those receiving conventional allo-SCT.[34] This phenomenon was also observed in our patients: none required platelet transfusion and only six of the 10 patients required a transfusion of red blood cells.

Seventy percent of the patients in our series achieved at least a partial response to mini-PBSC, and 30% achieved complete remission. Extensive chronic GVHD occurred only in patients displaying a partial response or complete remission; in contrast, all patients who showed no response to treatment had limited GVHD. Only one patient, who had shown complete remission, relapsed in the absence of chronic GVHD. A GVM effect must be responsible for this observation. Although the effect of GVM of pre-emptive donor lymphocyte infusion is appealing,[16,17,35] the high incidence of GVHD has limited its application.

Fludarabine combined with total body irradiation in our study resulted in successful engraftment before day 28 for all patients. There was no early treatment-related mortality and at a short median follow-up duration of about 1 year, all patients were still alive. Although there was no severe sepsis or fungal infection, the CMV reactivation rate in the early 6 months (70%) was high, and comparable to the rate documented in the literature.[36] No CMV disease was documented, however. All cases of CMV reactivation were responsive to ganciclovir alone or in combination with foscarnet. Such high CMV reactivation rate may be related to the delayed recovery of the CD3 and CD4 counts in the first 6 months.[26]

One of the drawbacks of this study is the lack of documentation of immune reconstitution by CD3 and CD4 count analysis; consequently, the relationship between immune reconstitution and events such as GVHD and CMV reactivation cannot be established. Despite the small number of patients and short follow-up period, we have shown that mini-PBSC using fludarabine and total body irradiation as a conditioning protocol is safe and effective. Studying more cases and increasing the follow-up duration are required to demonstrate the real benefit of this treatment in overall survival and long-term disease control. Moreover, issues such as optimal conditioning regimens, GVHD prophylaxis, and timing of transplantation need to be addressed by further studies.

Acknowledgements

The authors would like to thank the nursing staff of the Bone Marrow Transplantation Unit and Miss Lu for their assistance in this study.

References

1. Alexanian R, Dimopoulos M. The treatment of multiple myeloma. N Engl J Med 1994;330:484-9.
2. Bataille R, Harousseau JL. Multiple myeloma. N Engl J Med 1997; 336:1657-64.
3. Harousseau JL, Attal M. The role of autologous hematopoietic stem cell transplantation in multiple myeloma. Semin Hematol 1997;34(1 Suppl 1):61S-66S.
4. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. N Engl J Med 1996;335:91-7.
5. Fermand JP, Brechignac S. The role of autologous stem cell transplantation in the management of multiple myeloma. Pathol Biol (Paris) 1999;47:199-202.
6. Lenhoff S, Hjorth M, Holmberg E, et al. Impact on survival of high-dose therapy with autologous stem cell support in patients younger than 60 years with newly diagnosed multiple myeloma: a population-based study. Nordic Myeloma Study Group. Blood 2000;95:7-11.
7. Palumbo A, Triolo S, Argentino C, et al. Dose-intensive melphalan with stem cell support (MEL100) is superior to standard treatment in elderly myeloma patients. Blood 1999;94:1248-53.
8. Gahrton G, Tura S, Ljungman P, et al. Allogeneic bone marrow transplantation in multiple myeloma. European Group for Bone Marrow Transplantation. N Engl J Med 1991;325:1267-73.
9. Cavo M, Benni M, Cirio TM, Gozzetti A, Tura S. Allogeneic bone marrow transplantation for the treatment of multiple myeloma. An overview of published reports. Stem Cells 1995;13(Suppl 2): 126S-131S.
10. Bjorkstrand BB, Ljungman P, Svensson H, et al. Allogeneic bone marrow transplantation versus autologous stem cell transplantation in multiple myeloma: a retrospective case-matched study from the European Group for Blood and Marrow Transplantation. Blood 1996; 88:4711-8.
11. Goldschmidt H, Egerer G, Ho AD. Autologous and allogeneic stem cell transplantation in multiple myeloma. Bone Marrow Transplant 2000;25(Suppl 2):25S-26S.
12. Gahrton G, Tura S, Ljungman P, et al. Prognostic factors in allogeneic bone marrow transplantation for multiple myeloma. J Clin Oncol 1995; 13:1312-22.
13. Corradini P, Voena C, Tarella C, et al. Molecular and clinical remissions in multiple myeloma: role of autologous and allogeneic transplantation of hematopoietic cells. J Clin Oncol 1999;17:208-15.
14. Tricot G, Vesole DH, Jagannath S, Hilton J, Munshi N, Barlogie B. Graft-versus-myeloma effect: proof of principle. Blood 1996;87:1196-8.
15. Verdonck L, Lokhorst HM, Dekker AW, Nieuwenhuis HK, Petersen EJ. Graft-versus-myeloma effect in two cases. Lancet 1996;347:800-1.
16. Lokhorst HM, Schattenberg A, Cornelissen JJ, et al. Donor lymphocyte infusions for relapsed multiple myeloma after allogeneic stem-cell transplantation: predictive factors for response and long-term outcome. J Clin Oncol 2000;18:3031-7.
17. Orsini E, Alyea EP, Chillemi A, et al. Conversion to full donor chimerism following donor lymphocyte infusion is associated with disease response in patients with multiple myeloma. Biol Blood Marrow Transplant 2000;6:375-86.
18. Salama M, Nevill T, Marcellus D, et al. Donor leukocyte infusions for multiple myeloma. Bone Marrow Transplant 2000;26:1179-84.
19. Champlin R, Khouri I, Komblau S, Molidrem J, Giralt S. Reinventing bone marrow transplantation. Nonmyeloablative preparative regimens and induction of graft-vs-malignancy effect. Oncology (Huntingt) 1999;13:621-8,631,635-8,641.
20. Khouri IF, Keating M, Korbling M, et al. Transplant-lite: induction of graft-versus-malignancy using fludarabine-based nonablative chemotherapy and allogeneic blood progenitor-cell transplantation as treatment for lymphoid malignancies. J Clin Oncol 1998;16: 2817-24.
21. Childs RW. Nonmyeloablative allogeneic peripheral blood stem-cell transplantation as immunotherapy for malignant diseases. Cancer J 2000;6:179-87.

22. Giralt S, Estey E, Albitar M, et al. Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy. Blood 1997;89:4531-6.
23. Slavin S, Nagler A, Naparstek E, et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. Blood 1998;91: 756-63.
24. Feinstein L, Storb R. Nonmyeloablative hematopoietic cell transplantation. Curr Opin Oncol 2001;13:95-100.
25. Badros A, Barlogie B, Siegel E, et al. Improved outcome of allogeneic transplantation in high-risk multiple myeloma patients after nonmyeloablative conditioning. J Clin Oncol 2002;20:1295-303.
26. Badros A, Barlogie B, Morris C, et al. High response rate in refractory and poor-risk multiple myeloma after allotransplantation using a nonmyeloablative conditioning regimen and donor lymphocyte infusions. Blood 2001;97:2574-9.
27. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. Transplantation 1974;18:295-304.
28. Shulman HM, Sullivan KM, Weiden PL, et al. Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. Am J Med 1980;69:204-17.
29. Nuckols JD, Rasheed BK, McGlennen RC, Bigner SH, Stenzel TT. Evaluation of an automated technique for assessment of marrow engraftment after allogeneic bone marrow transplantation using a commercially available kit. Am J Clin Pathol 2000;113:135-40.
30. Koc S, Leisenring W, Flowers ME, et al. Thalidomide for treatment of patients with chronic graft-versus-host disease. Blood 2000;96: 3995-6.
31. Singhal S, Mehta J. Treatment of relapsed and refractory multiple myeloma. Curr Treat Options Oncol 2003;4:229-37.
32. Badros A, Tricot G, Toor A, et al. ABO mismatch may affect engraftment in multiple myeloma patients receiving nonmyeloablative conditioning. Transfusion 2002;42:205-9.
33. Maciej Zaucha J, Mielcarek M, Takatu A, et al. Engraftment of early erythroid progenitors is not delayed after non-myeloablative major ABO-incompatible haematopoietic stem cell transplantation. Br J Haematol 2002;119:740-50.
34. Weissinger F, Sandmaier BM, Maloney DG, Bensinger WI, Gooley T, Storb R. Decreased transfusion requirements for patients receiving nonmyeloablative compared with conventional peripheral blood stem cell transplants from HLA-identical siblings. Blood 2001;98:3584-8.
35. Helg C, Starobinski M, Jeannet M, Chapuis B. Donor lymphocyte infusion for the treatment of relapse after allogeneic hematopoietic stem cell transplantation. Leuk Lymphoma 1998;29:301-13.
36. Mohty M, Faucher C, Vey N, et al. High rate of secondary viral and bacterial infections in patients undergoing allogeneic bone marrow mini-transplantation. Bone Marrow Transplant 2000;26: 251-5.