Pre-transplant Disease Status is Important for an Improved Outcome of the Second Stem Cell Transplantation in the Myeloma Patients Receiving the First Autologous Stem Cell Transplantation

Ki-Seong Eom, Chang-Ki Min, Seok Lee, Yoo-Jin Kim, Sung-Yong Kim, Seok Goo Cho, Jong-Wook Lee, Woo-Sung Min and Chun-Choo Kim

Catholic Hemopoietic Stem Cell Transplantation Center, The Catholic University of Korea, Seoul, Korea

Background: Double autologous stem cell transplantation (ASCT) seems to be superior to a single ASCT, at least in the patients who did not achieve a 90% response after the first transplant. An allogeneic SCT with a dose-reduced conditioning regimen after ASCT and as part of the initial therapy, might be a feasible and highly effective approach. The aim of this study was to determine the prognostic factors that are associated with the outcome of multiple myeloma (MM) patients who had received a second transplant.
Methods: From April 1996 to December 2004, 38 MM patients, who had previously received high-dose melphalan (200 mg/m^2) with autologous stem cell support, underwent a second transplant. Following the 1st ASCT, 24 patients received a second ASCT and 14 received a tandem reduced-intensity conditioning allogeneic stem cell transplantation (RIST) from their HLA-matched siblings.
Results: The 3-year estimated PFS and overall survival (OS) from the time of the first ASCT were 25.2% and 77.6%, respectively. The median PFS and OS were 26 months (95% CI, 23～29) and 60 months (95% CI, 44～76), respectively. The disease status (a CR *vs.* PR or less) at the second transplant was be the most powerful factor for improving the PFS (P=0.001, hazard ratio 5.8, 95% CI 2.1～16.1).
Conclusion: Patients whose disease is sensitive to chemotherapy and who obtain a CR after a single transplantation might benefit the most from a second transplant. ***(Korean J Hematol 2006;41:36-40.)***

Key Words: Multiple myeloma, Tandem stem cell transplantation, Reduced-intensity allogeneic transplantation, Autologous stem cell transplantation

INTRODUCTION

The use of autologous stem cell transplantation (ASCT) after intensive chemotherapy or chemo-radiotherapy is part of the initial treatment plan for patients with multiple myeloma (MM). Although a large randomized trial[1] previously demonstrated superior response rates and survival compared with conventional therapy, the disease eventually recurs and relapse is still the main reason for treatment failure after ASCT. In an attempt to prolong the duration of the response, many studies have evaluated ASCT combined with a

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교신저자 : 민창기, 서울시 영등포구 여의도동 62번지
㉾ 150-713, 여의도성모병원 내과 혈액분과
Tel: 02-3779-1124, Fax: 02-780-3132
E-mail: ckmin@catholic.ac.kr

Correspondence to : Chang-Ki Min, M.D.
Division of Hematology, Department of Internal Medicine, St. Mary's Hospital
#62 Youido-dong, Yeongdeungpo-gu, Seoul 150-713, Korea
Tel: +82-2-3779-1124, Fax: +82-2-780-3132
E-mail: ckmin@catholic.ac.kr

subsequent transplant using either an auto-graft or allo-graft.[2-5] Recent results from an IFM94 trial[6] showed that a double ASCT is superior to a single ASCT, at least in patients who did not achieve a 90% response after the first transplant. An allogeneic SCT with a dose-reduced conditioning regimen after an ASCT as part of the initial therapy might be a feasible and highly effective approach.[4,5] The aim of this study was to determine the prognostic factors associated with the outcome of MM patients who had received a second transplant. The disease status prior to the second transplant was found to be the most significant factor for predicting the progression-free survival (PFS). The second transplant mostly benefited those patients who had achieved complete response after undergoing the first ASCT.

PATIENTS AND METHODS

From April 1996 to December 2004, 38 MM patients, who had previously received high-dose melphalan (200mg/m^2) with autologous stem cell support, underwent a second transplant. Due to referral reasons, the patient preference and the availability of HLA-matched siblings in the trials, 24 patients received a second ASCT and 14 received a tandem reduced-intensity conditioning allogeneic stem cell transplantation (RIST) from HLA-matched siblings after the first ASCT. In this study, melphalan (140mg/m^2)+TBI (1,000 cGy) were used as the conditioning regimen in those patients undergoing ASCT as a second transplant, while those undergoing RIST received fludarabine (30mg/m^2/day) for 4 days and melphalan 70mg/m^2/day on two consecutive days before infusing the G-CSF mobilized peripheral blood mononuclear cells. Cyclosporine A and methotrexate or mycophenolate mofetil were administered to the patients in order to prevent graft-versus-host disease (GVHD).[7] Acute GVHD was graded on a four-point scale (I indicates mild disease, and IV severe disease),[8] and chronic GVHD was classified as either limited or extensive, as described elsewhere.[9] The responses were classified according to the standard criteria.[10] The duration of the PFS was calculated for all patients from the date of the first transplant to the time of progression, relapse or death.

RESULT

There were 20 male patients (52.6%), and the median age was 48 years (range, 32～59). Most patients had a high tumor burden, with 36 patients (94.8%) having Durie-Salmon stage III. Seventeen patients (44.7%) patients had advanced

Table 1. Transplant characteristics of the second transplant

	Allogeneic SCT (n=14)	Autologous SCT (n=24)	*P*
Median time from the first to the second transplant, months (range)	5.5 (4～10)	4.5 (3.5～7)	NS
No. of infused CD34 cells (10^6/kg), median (range)	5.1 (0.9～17.0)	7.8 (3.6～15.4)	NS
Median time to ANC $>0.5\times10^9$/L, days (range)	12 (10～14)	13 (8～19)	NS
Median time to platelet count $>20\times10^9$/L, days (range)	13 (0～18)	16 (10～25)	NS
Response to 1st ASCT CR/PR/MR/PD	8/2/3/1	15/8/1/0	NS
Median follow-up time, months (range)	30 (9～42)	31.5 (10～71)	NS

Abbreviations: ANC, absolute neutrophil count; CR, denotes complete remission; PR, partial response; MR, minimal response; PD, progressive disease.

bone disease. Thirty-nine percent, 21.1%, 2.6% and 23.7% of the patients had immunoglobulin G (IgG), IgA, IgM and light chain disease, respectively. The median time from the first ASCT to the second transplant was 5 months (range, 3.5～10). At the time of the second transplant, 23 patients (60.5%) had achieved complete remission (CR) after the first ASCT. Ten patients (26.4%) achieved a partial response (PR), 4 (10.5%) a minimal response (MR) and 1 (2.6%) experienced progressive disease (PD). Table 1 shows the characteristics of the second transplant. The median time to granulocyte and platelet engraftment was similar in the two groups. An analysis of chimerism revealed all patients with RIST to be 'fully donor'. At a median follow-up of 31.5 and 30 months, 13 out of 24 patients (54.2%) relapsed or progressed in the ASCT group while 5 out of 13 patients (38.4%) who could be evaluated in the RIST group did. Four out of 5 patients who relapsed after RIST had extramedullary plasmacytomas without a BM relapse. There were 2 cases (14.2%) of grade II-IV acute GVHD. Limited and extensive chronic GVHD occurred in 1 (7.7%) and 9 (69.2%) out of the 13 evaluable patients, respectively. The median follow-up from the first ASCT for those patients still alive at the last follow-up was 32 months (range 9～98). The 3-year estimated PFS and overall survival (OS) from the time of the first ASCT were 25.2% and 77.6%, respectively. The median PFS and OS were 26 months (95% CI, 23～29) and 60 months (95% CI, 44～76), respectively. Multivariate analysis using a Cox proportional hazard regression model revealed the disease status (a CR *vs.* PR or less) at the second transplant to be the most powerful factor for improving the PFS (P=0.001, hazard ratio 5.8, 95% CI 2.1～16.1). Fig. 1 shows the PFS according to the disease status prior to the second transplant. The median PFS was 43 months (95% CI,

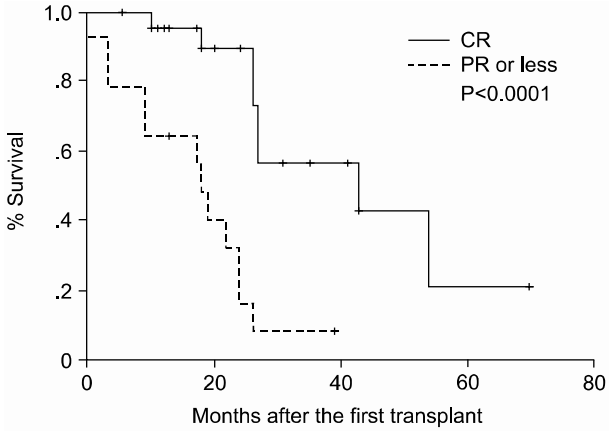

Fig. 1. Progression-free survival of all patients (n=38) who received the first autologous stem cell transplant according to the disease status prior to the second transplant.

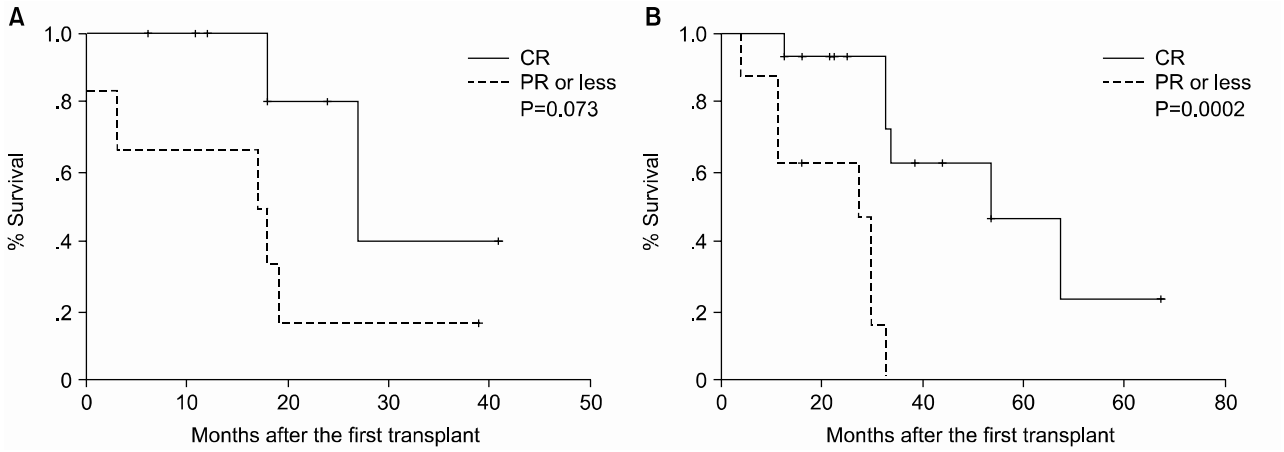

Fig. 2. Progression-free survival of patients (A; n=14) who received the reduced-intensity conditioning allogeneic stem cell transplantation and those (B; n=24) who underwent the autologous stem cell transplant according to the disease status before the second transplant.

8～78) in the patients who achieved a CR and 18 months (95% CI, 15～21) in those who did not (P=0.0001 by the log-rank test). While there was a significant difference in the PFS, the median OS did not differ (CR: 60 months; PR or less: 50 months; P=0.144). Fig. 2A and B show the PFS in patients who received the RIST or ASCT as the second transplant, respectively. The difference in the PFS according to the disease status was marginally significant in those patients who had received RIST (P=0.073). However, the difference in the PFS was significant in those who had undergone ASCT as the second transplant (P=0.0002).

DISCUSSION

It was reported that the benefit of a second course high-dose therapy depends on its capacity to achieve a CR in MM patients who did not achieve a CR after the first ASCT.[6] The PFS or OS in the patients who achieved a CR after the first ASCT were similar to those patients who achieved a PR after the first ASCT and went on to achieve a CR after the second transplant.[11] Alexanian et al[12] reported that the survival was similar for patients who had converted from a PR to CR after high-dose therapy and patients who achieved a CR after only standard therapy, even though the CR rates were obviously different for the high-dose and conventional treatments. Furthermore, Blade et al[13] reported that the outcome for patients who achieved a PR after ASCT was equivalent to that of patients who were conventionally treated for a PR.

In contrast, in our patients, the only prognostic factor for a response was a CR before the second transplant. These results showed that the second transplant did not improve the outcome of patients who achieved a PR or less after the first ASCT conditioned with melphalan 200mg/m^2. In contrast, patients who achieved a CR after the first ASCT significantly benefited by the second transplant. The more the patients obtained molecular remission after the first transplant, the better their PFS.[14] Whether or not the capacity of a second transplant to induce a CR in patients attaining a PR or less after the first transplant was not found to be crucial to the efficacy of the tandem transplant in our patients. The influence of a CR before the second transplant on the PFS was similar regardless of whether they had undergone ASCT or RIST as the second transplant. However, there was a larger difference in those patients receiving ASCT than in those receiving RIST. These results indicate the potential and durable graft-versus-myeloma effect of an allograft in some patients with chemoresistant disease. Information on the impact of a minimal residual disease (MRD) evaluation on the clinical outcome and its role in the clinical management of molecular monitoring in MM after the first ASCT was unavailable. This study did not evaluate MRD using polymerase chain reaction or flow cytometry.[15]

At the stage of MRD, the second transplant may provide an effective modality for eradicating the tumor cells remaining after the first ASCT. It appears that at the stage of MRD following high-dose melphalan and ASCT, a small tumor burden can be more easily eliminated by the second transplant using either ASCT or RIST. Therefore, patients whose disease is sensitive to chemotherapy and who obtain a CR after a single transplantation might most benefit from a second transplant.

요 약

배경: 2회 자가조혈모세포이식(ASCT)은 조혈모세포이식을 1회 시행하는 것보다 최소한 첫 이식에서 90% 이상 반응을 보인 환자에서 우수한 치료성적을 보이는 것으로 알려져 있다. 초치료의 일환으로 자가조혈모세포이식 후 저용량 전처치를 이용한 동종조혈모세포이식은 안전하고 매우 효과적인 치료법이다. 본 연구에서 저자들은 조혈모세포이식을 2회 받은 다발성골수종 환자의 치료성적과 관련된 예후인자를 결정하기 위한 분석을 시행하였다.

방법: 1996년 4월부터 2004년 12월까지 가톨릭조

혈모세포이식센터에서 고용량 melphalan (200mg/m^2)을 전처치로 자가조혈모세포이식을 받은 후 두 번째 조혈모세포이식을 받은 38명의 다발성골수종 환자를 대상으로 하였다. 1차 자가조혈모세포이식 후 24명은 2차 조혈모세포이식으로 자가조혈모세포이식을 받았고, 14명은 HLA가 일치하는 형제 공여자로부터 저용량 전처치를 이용한 동종조혈모세포이식을 받았다.

결과: 1차 조혈모세포이식 후 3년 추정 무진행생존율과 전체생존율은 각각 25.2%와 77.6%이었다. 무진행생존율과 전체생존율의 중앙값은 각각 26개월(95% CI, 23～29)과 60개월(95% CI, 44～76)이었다. 2차 이식 당시의 질환의 상태(완전반응 versus 부분반응 혹은 그 이하의 반응)가 무진행생존율의 향상에 영향을 미치는 가장 강력한 인자로 나타났다 (P=0.001, hazard ratio 5.8, 95% CI 2.1～16.1).

결론: 항암화학치료에 잘 반응하고 1차 이식에서 완전반응을 보인 다발성골수종환자가 2차 이식으로 가장 큰 효과를 얻을 수 있었으며, 이 효과는 자가 및 동종조혈모세포이식에서 공통적으로 발견되었다.

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