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<th>Hematopoietic stem cell transplantation in the department of hematology, fukushima medical university</th>
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HEMATOPOIETIC STEM CELL TRANSPLANTATION IN
THE DEPARTMENT OF HEMATOLOGY,
FUKUSHIMA MEDICAL UNIVERSITY

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Abstract : From 1996 to the end of 2009, a total of 114 cases of hematopoietic stem cell transplantation were performed in the Department of Hematology, Fukushima Medical University. We report here a general overview of our results. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) was performed in 37 cases of acute leukemia, 10 of myelodysplastic syndrome, 5 of aplastic anemia, and 5 others. The 5-year survival rate with allo-HSCT was 51.1%. Autologous hematopoietic stem cell transplantation (auto-HSCT) was performed in 34 cases of malignant lymphoma, 15 of multiple myeloma, and 8 others. The 5-year patient survival rate was 75.2% with malignant lymphoma and 46.7% with multiple myeloma. These results are comparable to those from a nationwide survey in Japan, confirming that our hospital has attained a creditable level as a transplantation center.

Key words : Allogenic stem cell transplantation, Autologous stem cell transplantation, Survival curves

INTRODUCTION

Hematopoietic stem cell transplantation is becoming established as a treatment for refractory blood diseases, with the aim of achieving a cure or prolonging survival. According to a report by the Japan Society for Hematopoietic Cell Transplantation, the number of transplantations performed in Japan had reached 49,100 by 20081). The total number performed in Fukushima Prefecture was 359,269 of which were carried out in our department and the department of pediatrics at our hospital. Our department began autologous hematopoietic stem cell transplantation (auto-HSCT) in 1996 and allogeneic hematopoietic stem cell transplantation (allo-HSCT) in 1999. By the end of 2009, we had performed a total of 114 hematopoietic stem cell transplantations, the results of which we report here.

METHODS

The subjects were 114 patients who underwent hematopoietic stem cell transplantation (allo-HSCT, n=57; auto-HSCT, n=57) in our department between July 1996 and December 2009.
Using medical records of the above transplantation patients, we surveyed age and disease duration at the time of transplantation, stem cell source, occurrence of graft-versus-host disease (GVHD), complications, and cause of death. The observation period lasted until the end of June 2010. Survival rates were calculated using the Kaplan-Meier method, and the log-rank test was used to test for statistical significance.

RESULTS

1. Trends in numbers of transplantations (Fig. 1)

Auto-HSCTs were started in 1996 and allo-HSCTs in 1999. The number of transplantations increased each year, peaking in 2009 with 17 transplantations, including 8 auto-HSCTs and 9 allo-HSCTs.

To date, we have not performed any syngeneic HSCTs.

2. Allo-HSCT

The clinical characteristics of 57 patients who underwent an allo-HSCT are shown in Table 1. Median patient age at the time of transplantation was 37 years. Fifty-two patients (91%) had hematologic malignancies, and the remaining 5 had aplastic anemia (AA). The most common disease was acute myeloid leukemia (n=24, 42%), followed by acute lymphoblastic leukemia (n=13, 23%). The stem cell source was bone marrow in 35 cases (61%) and peripheral blood stem cells (PBSCs) in 22 (39%). Nearly all bone marrow transplantations (BMTs) were from unrelated donors (n=33). HLA-mismatched transplantations (n=14) were performed with one-locus mismatch. Of 24 cases of transplantation from related donors, 5 were mismatched. They included 2 cases of HLA-A mismatches and 3 of HLA-DR locus mismatches. Nine of the 33 unrelated bone marrow transplantations were HLA-mismatched transplantations, 8 of which were single HLA-DRB1 mismatches.

The conditioning regimen before HSCT was a myeloablative stem cell transplantation in 43 patients (75%) and a non-myeloablative stem cell transplantation in 14 (MDS, n=6; AA, n=4; malignant lymphoma, n=2; AML, n=1; myelofibrosis, n=1) (25%). Myeloablative conditioning regimens included either total body irradiation (TBI)-based regimens or non-TBI-based regimens. TBI-based regimens mainly consisted of cyclophosphamide (120 mg/kg) plus fractionated TBI (12 Gy), whereas non-TBI-based regimens included busulfan (16 mg/kg) plus cyclophosphamide (120 mg/kg). Nonmyeloablative conditioning regimens consisted of fludarabine (125 mg/kg) based regimens with or without low-dose TBI (4 Gy). To prevent GVHD, cyclosporine A (CyA + methotrexate (MTX) was used in HLA-matched related HSCTs and tacrolimus (TAC)+MTX was used in one-locus-mismatched related HSCTs and unrelated bone marrow transplantations. Engraftment was obtained in 51 (94%) of 54 patients, the other 3 died within 21 days of transplantation. The 3 cases of graft rejection all involved unrelated bone marrow transplantations, i.e., 1 case each of acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and myelodysplastic syndrome.
HEMATOPOIETIC STEM CELL TRANSPLANTATION

Table 1. Clinical characteristics of 57 patients undergoing allogeneic hematopoietic stem cell transplantation

<table>
<thead>
<tr>
<th>Total number</th>
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<tr>
<td>Median age (range)</td>
<td>37 (17-60)</td>
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<tr>
<td>Sex (M/F)</td>
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<td>Conditioning regimen</td>
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<tr>
<td>Diagnosis</td>
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<tr>
<td>AML</td>
<td>24</td>
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<tr>
<td>First remission</td>
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<td></td>
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<td>Second remission</td>
<td>6</td>
<td>CyA+MTX 22</td>
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<td>TAC+MTX 34</td>
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<tr>
<td>ALL</td>
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<td>CyA+PSL 1</td>
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<tr>
<td>First remission</td>
<td>4</td>
<td>Engraftment 51</td>
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<tr>
<td>Second remission</td>
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<td>Acute GVHD</td>
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<td>Fourth remission</td>
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<tr>
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<td>Grade I 9</td>
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<tr>
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<td>RA</td>
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<tr>
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<td>33</td>
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</tr>
<tr>
<td>PBSCs</td>
<td>22</td>
<td>TRC 13</td>
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AML; Acute myeloid leukemia, ALL; acute lymphoblastic leukemia, MDS; myelodysplastic syndrome, RA; refractory anemia, RARS; refractory anemia with ringed sideroblasts, RAEB; refractory anemia with excess blasts, CML; chronic myelogenous leukemia, ML; malignant lymphoma, DLBCL; diffuse large B-cell lymphoma, MCL; mantle cell lymphoma, MF myelofibrosis, AA; aplastic anemia, BM; bone marrow, PBSCs; peripheral blood stem cell, CyA; cyclosporine, MTX; methotrexate, TAC tacrolimus, PSL; prednisolone, NE; not evaluated, PD; progressive disease, TRC; transplantation related complications

(MDS). Two of these 3 cases were transplantations at an advanced stage. Acute GVHD was seen in 20 (37%) of 54 evaluable cases, of which acute GVHD of grade II or higher was seen in 11 cases (20%). Chronic GVHD was seen in 13 (28%) of 47 evaluable cases. Twenty-seven patients (47%) died during the observation period. Causes of death were transplantation-related complications in 13 patients (48%) and relapse or progression of the original disease in 14 (52%). Causes of death among the transplantation-related deaths were infection in 5 cases, thrombotic microangiopathy in 1, bronchiolitis obliterans in 1, GVHD in 2, veno-occlusive disease in 2, and other causes in 2.

3. Survival rate after allo-HSCT

The overall 5-year survival rate for allo-HSCT was 51.1% (Fig. 2). As of June 2010, all allo-HSCT patients are alive in continuous complete remission with the exception of 1 patient with CML. Figure 3 shows the survival curve for time after transplantation in acute leukemia patients. Transplantation
was for relapse or refractory disease in 10 (42%) of 24 AML patients, and 5 (38%) of 13 ALL patients. The five-year survival rate was 55.4% in cases of transplantation in complete remission, and 13.3% in cases of relapse or refractory disease. Figure 4 shows the survival curves by donor. Five-year survival was 39.7% with HSCT from a related donor, rising to 60.3% with HSCT from an unrelated donor. This difference, however, was not statistically significant ($P=0.35$).

4. Auto-HSCT

The clinical characteristics of patients with auto-HSCT are shown in Table 2. The underlying disease was malignant lymphoma in 34 cases, multiple myeloma in 15, and other diseases in 8 (AML, $n=6$; chronic myelogenous leukemia (CML), $n=1$; malignant peripheral nerve sheath tumor, $n=1$). The median age of malignant lymphoma patients was 47 years, with diffuse large B-cell lymphoma being the most common subtype diagnosed in 16 patients (47%). Nine patients (26%) died during the observation period, with relapse or progression of the original disease as the cause of death in all cases. The median age of multiple myeloma patients was 57 years. Seven patients (47%) showed amyloidosis complications, 4 of whom had cardiac amyloidosis with severe diastolic heart failure or life-threatening ventricular tachycardia. Six patients (35%) died during the observation period, with relapse or progression of the original disease as the cause of death in 5 cases and ventricular tachycardia in 1. Autologous peripheral blood stem cell transplantation was performed in 6 AML patients. All transplantations were performed in the first remission, and all patients were alive in continuous complete remission as of June 2010.

5. Survival rate after auto-HSCT

The 5-year survival rate of malignant lymphoma patients was 75.2% (Fig. 5), while that of multiple
myeloma patients was 46.7% (Fig. 6).

DISCUSSION

The 5-year survival rate with allo-HSCT in our department was 51.1%, while that for all transplants including, auto-HSCT, was 50.9% in a 2009 survey reported by the Japan Society for Hematopoietic Cell Transplantation. Thirty-seven of the 57 who underwent allo-HSCT in our department were leukemia patients. Considering that 15 of 37 acute leukemia patients were transplanted for relapse or progressive disease, and that the source of transplanted cells was an unrelated donor in 33 of the 57
patients, the 5-year survival rate for allo-HSCT in our department was a notable achievement, indicating that the standard of medical transplantations in our department would appear to have reached a proficient level. According to a national survey, 5-year survival rates for AML patients in first remission, including related and unrelated transplantations, ranged from 50.2% to 56.3%. Five-year survival rates in ALL were 46.9-61.1%. In our department, the 5-year survival rate for acute leukemia patients in remission, including both AML and ALL, was 55.4%. However, considering that only 12 of 22 transplantations were in the first remission, with all others in the second or later remission, the results of allo-HSCT among acute leukemia patients in remission in our hospital seem creditable. In the national survey, 5-year survival rates with transplantations in refractory or relapsed disease were 10-20%. A similar difficulty involving transplantations for refractory or relapsed disease was experienced in our department.

Transplantations in our department were HLA-mismatched in 14 of 57 patients. Although most of the HLA-mismatched transplantations were single HLA-DRB1 mismatches, they had no major effects on the occurrence of acute GVHD\(^{4,5}\). Similarly, we observed no increase in acute GVHD among our single locus mismatch transplantation patients.

In our allo-HSCTs, the 5-year survival rate tended to be higher with unrelated than with related
transplants. Similar results with related and unrel-
ated bone marrow transplants have been reported
in other high-risk patients. In ALL, disease-free
survival with transplantation performed in the first
remission using unrelated bone marrow transplant-
ation was reportedly not inferior to that with related
bone marrow transplantation. The reason for
this is thought to be that, despite the high therapy-
related mortality among unrelated transplants,
relapse in high-risk patients, including those with
ALL, is suppressed by the action of a stronger graft-
versus-leukemia effect. The reason for the poor
results with related transplantations in our patients
may have been that 8 of the 12 leukemia patients
who received related transplants experienced a
relapse or progression of the original disease follow-
ing transplant. In addition, all our unrelated trans-
plantations cases were bone marrow transplanta-
tions, in which TAC was used to prevent GVHD.
In contrast, 22 of 24 of our related transplantations
cases were peripheral blood stem cell transplanta-
tions in which CyA was used to prevent GVHD.
Thus, we cannot rule out the possibility that the dif-
ference in our results with unrelated and related
transplantations reflected differences in GVHD pro-
phylaxis (TAC vs CyA) or stem cell sources (BMT
vs PBSCT). In recent years, non-myeloablative
stem cell transplantation using reduced-intensity
pretransplantation regimens has become widely
used. We have also conducted non-myeloabla-
tive stem cell transplantation in 14 patients, 11 of
whom are surviving in continuous complete remis-
sion as of June 2010. Though the large numbers of
MDS and AA cases are thought to be one reason for
the good results, 2 of the 3 patients who died after
transplantation expired from progression of the origi-
nal disease. The small number of treatment-
related deaths is therefore a major advantage of non-
myeloablative stem cell transplantation, with patient
selection and treatment also being highly important.

According to a national survey, the 5-year sur-
vival rate with auto-HSCT for malignant lymphoma
is 59.1%, and our hospital exceeded those results.
The high quality of our medical transplantations is
also supported by the fact that we did not encounter
a single transplantation-related death. In recent
years, attempts have been made to eliminate malig-
nant cells from the graft with the combined use of
rituximab during mobilization and the collection of
peripheral blood stem cells (in vivo purging). We
also performed in vivo purging with rituximab dur-
ing the mobilization and collection of peripheral
blood stem cells in 2 patients with malignant lym-
phoma, both of whom were surviving in continuous
complete remission as of June 2010.

According to a national survey, the 5-year sur-
vival rate with auto-HSCT for multiple myeloma is
51.2%. The fact that our hospital was somewhat
below those results is mainly attributable to the fact
that 47% of patients experienced complications with
amyloidosis with organ damage. However, our
patient who had life-threatening ventricular tachy-
cardia underwent auto-HSCT and obtained long-
term survival, therefore, we believe that auto-HSCT
should be performed aggressively even in patients
with amyloidosis complications.

According to a report by the Japan Marrow
Donor Program, 133 patients in Fukushima Prefec-
ture were registered and had received transplan-
tations as of June 2010, but only 62 underwent trans-
plantations inside Fukushima Prefecture. One
reason for this may be that our hospital is the only
institution in the prefecture approved by the Japan
Marrow Donor Program to perform transplantations.
The present analysis confirmed that the transplanta-
tion results at our hospital are creditable. Our next
task is to increase the number of transplant facilities
in Fukushima Prefecture while maintaining this
level of quality.

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REFERENCES

1. The Japan Society for Hematopoietic Cell Trans-
plantation. Annual Report of National Survey
2009. (in Japanese)
2. McSweeney PA, Niederwieser D, Shizuru JA, Sand-
daier BM, Molina AJ, Maloney DG, Chaucy
TR, Gooley TA, Hegenbart U, Nash RA, Radich J,
Wagner JL, Minor S, Appelbaum FR, Bensinger
WI, Bryant E, Flowers ME, Georges GE, Grumet
FC, Kiem HP, Torok-Storb B, Yu C, Blume KG,
Storb RF. Hematopoietic cell transplantation in
older patients with hematologic malignan-
cies: replacing high-dose cytotoxic therapy with
graft-versus-tumor effects. Blood, 97: 3390-


