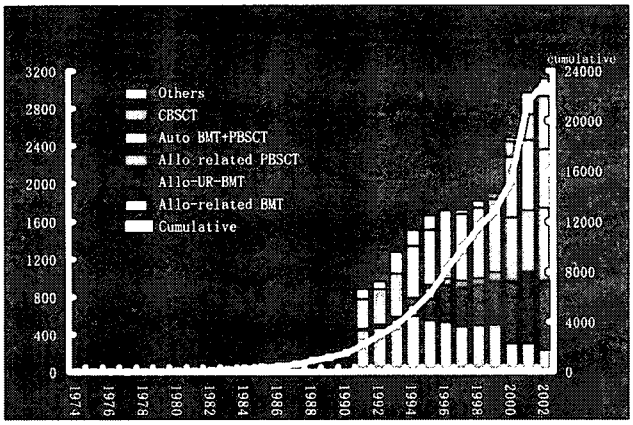


Figure 1 Status of HSCT in Japan. CBSCT, cord blood stem cell transplant; BMT, bone marrow transplant; PBSCT, peripheral blood stem cell transplant; Auto, autologous; Allo, allogeneic; UR-BMT, unrelated donor BMT.

Current Status and Clinical Outcomes of Hematopoietic Stem Cell Transplantation in Japan

Allogeneic Transplant in Japan

Figure 1 shows the annual and cumulative case numbers transplanted from different stem cell sources in Japan; data were obtained by compiling the nationwide case report system of the Japan Society of Hematopoietic Cell Transplantation (JSHCT; capture rate ~70%),[18] the JMDP (capture rate ~100%), the Japan Cord Blood Network (JCBBN) (capture rate near 100%), the nationwide peripheral blood stem cell donor follow-up system conducted by JSHCT (capture rate ~100%), and grant studies supported by the Ministry of Health, Labor and Welfare of Japan. Transplants numbered approximately 3,000 in 2002, and 75% of them were allogeneic, including 8% bone marrow transplants (BMTs) and 25% peripheral blood stem cell transplants (PBSCTs) from related donors, 24% BMTs from unrelated donors, and 19% cord blood stem cell transplants (CBSCTs).

Bone Marrow Transplantation From Unrelated Donors and From Genetically Matched Sibling Donors

Outcomes of transplants from each stem cell source are summarized in Tables 1 through 4. The probability of overall 5-year survival for patients who received bone marrow from HLA-matched siblings, whose data were collected from 331 departments participating in the JSHCT, was separately analyzed for adults (age ≥16) and children (age <16). The probability of 5-year disease-free survival (DFS) of patients who received bone marrow from 6/6 HLA serologically matched unrelated volunteer donors provided an opportunity for bulk analysis. The data were collected from departments registered with the JMDP. As indicated in Tables 1 and 2, the 5-year Kaplan-Meier survival for patients transplanted from unrelated donors was equivalent to that of patients who received marrow grafts from HLA genotypically matched siblings for indications of acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL), and myelodysplastic syndrome (MDS). The survival of chronic myelogenous leukemia (CML) patients transplanted in chronic phase from unrelated donors was lower than that for patients transplanted from siblings but was equivalent for patients transplanted at more advanced stages of this disease. For severe aplastic anemia, the survival rate of patients transplanted from unrelated donors was lower than that for HLA genotypically identical siblings, but outcomes were comparable for patients transplanted in relatively early stages of the disease (low-risk BTF group). From these outcomes, we consider BMT from 6/6 HLA serologically matched, unrelated donors as well as from HLA genotypically matched siblings to be the "gold standard" for stem cell transplants.

Table 1 Outcomes of Matched Sibling and Unrelated Donor BMT*

	5-Year Survival		
	Matched Sibling BMT*		Unrelated Donor BMT†
	Adult	Child	
AML			
1 CR	67 (474)	76 (157)	68 (253)
2 CR	59 (171)	69 (27)	52 (190)
> 3 CR	42 (18)	50 (2)	27 (48)
Relapse	20 (224)	49 (48)	10 (278)
ALL			
1 CR	56 (377)	73 (132)	59 (316)
2 CR	26 (84)	39 (27)	46 (210)
> 3 CR	18 (17)	39 (27)	28 (54)
Relapse	16 (154)	13 (95)	15 (227)

Abbreviations: AML, acute myelogenous leukemia; CR, complete remission; ALL, acute lymphocytic leukemia.
*Data from JSHCT, December 2001.
†Data from JMDP, October 2002.

Table 2 Outcomes of Matched Sibling and Unrelated Donor BMT

	5-Year Survival		
	Matched Sibling BMT*		Unrelated Donor BMT†
	Adult	Child	
CML			
1 CP	73 (555)	78 (41)	52 (546)
2 CP	34 (26)	0 (1)	41 (51)
Acc	40 (55)	67 (3)	37 (115)
BC	28 (51)		8 (78)
MDS			
—	65 (167)	81 (39)	57 (75)
—			80 (5)
—	39 (133)	46 (22)	38 (68)
—	35 (167)	51 (35)	31 (93)
—	41 (44)	45 (17)	48 (21)
Aplasia			
Child	93 (19)	90 (89)	Low-risk BTF 73 (97)
Adult	87 (37)	53 (19)	High-risk BTF 56 (125)

Abbreviations: CML, chronic myelocytic leukemia; CP, chronic phase; Acc, accelerated phase; BC, blastic crisis; MDS, myelodysplastic syndrome; BTF, blood transfusion.
*Data from JSHCT, December 2001.
†Data from JMDP, October 2002.

Allogeneic PBSCT Among Siblings for Advanced Leukemia and the Outcome of CBSCT After 2001

Outcomes of PBSCTs from related donors and of CBSCTs were compared to the excellent results obtained with genotypically matched siblings and genotypically compatible matched unrelated donors. PBSCTs from HLA-matched siblings showed 5-year DFS equivalent to that of BMT when transplant was undertaken at an early stage of leukemia (first complete remission of acute leukemia and first chronic phase of CML) and improved survival when transplanted at an advanced stage of the disease (Table 3). Comparing unrelated BMT and CBSCT in patients younger than 15 years, the former is advantageous in terms of 3-year DFS but the difference became smaller for transplants performed after 2001 (Table 4).

Table 3 Outcomes of BMT Versus PBSCT From Matched Siblings

	5-Year DFS (n)	
	BMT	PBSCT
AML		
1 CR	59.8 (192)	61.5 (58)
Other	35.5 (182)*	40.0 (91)*
ALL		
1 CR	56.7 (152)	56.8 (52)
Other	15.2 (88)	26.5 (39)
CML		
1 CP	72.7 (259)	72.7 (61)
Other	36.2 (53)	67.2 (26)

Abbreviation: DFS, disease-free survival.
Data from JSHCT, December 2003.
*Three-year DFS.

Outcomes of Allogeneic Stem Cell Transplantation and Genetic Homogeneity in Japanese

Table 5 summarizes the frequency of grades III–IV acute GVHD after allogeneic BMT from related and unrelated donors according to HLA match status among Japanese patients. The frequency of grades III–IV acute GVHD was 8.1% among 4,701 HLA genotypically identical sibling transplants and 13.1% among 1,371 6/6 HLA serologically matched unrelated donors. These frequencies were almost the same as in our earlier reports[6,19,20] but lower than that of other cohorts.[5,21] Since most of the cases transplanted from 1991 to 1999 received cyclosporine-based GVHD prophylaxis, we consider the low incidence of severe acute GVHD to be a reflection of the genetic homogeneity of Japanese people.

Indications for Allogeneic HSCT

The potential number of new candidates for allogeneic stem cell transplants in Japan was estimated from the current annual number of patients who initiated a donor search with

Table 4 Outcomes of Unrelated Donor BMT Versus Unrelated Donor CBSCT

	3-Year DFS (n)	
	UR-BMT	UR-CBSCT
Transplanted before 2000	50.2 (347)	34.1 (139)
Transplanted after 2001	65.9 (116)	53.5 (96)

NOTE. For patients under age 15, both standard and high risks were included.
Abbreviation: UR, unrelated donor.
Data from *Cord Blood Bank Now*, Vol 19, September 2004.

Table 5 Outcome of Allogeneic CD34$^+$ Cell Transplantation in Japan

Rate of engraftment	82.0%
Rate of acute GVHD (>grade-3)	8.4%
Overall survival	27.4%
Disease-free survival	18.5%
Cause of death	
Infection	38%
Relapse	30%
Other TRM	22%
VOD	5%
GVHD	5%

Abbreviations: TRM, transplant-related mortality; VOD, veno-occlusive disease; GVHD, graft-versus-host disease.
Data from Kato et al.[14]

the JMDP. The number of patients registered with the JMDP was 1,536 in 2000, 1,603 in 2001, and 1,792 in 2002 (when the JCBBN began activity and imatinib was available for CML; therefore, the effects of these factors were excluded). The annual number of unrelated BMTs facilitated through the JMDP was 715 in 2000, 749 in 2001, and 739 in 2002. Thus, some 800 patients remain to be transplanted from donors other than HLA genotypically identical siblings, 6/6 HLA-matched unrelated donors, or HLA closely matched cord blood. In general, the JMDP approves registration only for patients younger than 50 years of age. The number of cases awaiting transplantation would double if transplant eligibility was extended to patients under 65 so that approximately 1,500 new patients would appear each year as candidates for allogeneic transplantation from alternative stem cell sources other than HLA-matched related or unrelated donors, or HLA closely matched cord blood, even if eligibility were restricted to patients younger than 65 with leukemia, myelodysplastic syndrome, and other marrow failure syndromes.

Alternative Stem Cell Sources

Transplants From HLA Single Locus Mismatched Family Members and 6/6 HLA-Matched Unrelated Donors

Following a preliminary survey of the experiences of local transplant teams,[12], Kanda et al recently analyzed 142 patients who underwent allogeneic HSCT from HLA-mismatched family members and compared the outcome to that obtained from 2,805 transplants among HLA-matched siblings and to 1,002 transplants from 6/6 HLA-matched unrelated donors.[22] Among 2,947 adult (age >16) patients who received stem cell transplantation from family donors for the first time between 1991 and 2000 for CML, AML, ALL, and MDS, and for whom serologic HLA datasets for HLA-A, -B, and DR loci were fully available, 112 received the transplants from donors with a single locus mismatch (70 class 1 mismatch; 42 class 2 mismatch; 70 bidirectional mismatch; 15 mismatch at graft-versus-host vector alone; 27 host-versus-graft-vector alone; 89 BMT; 23 PBSCT), and the other 30 patients received the stem cells from donors with more than two mismatched loci. Ninety-one percent of 2,947 patients received cyclosporine-based GVHD prophylaxis. The study included a control group provided by the JMDP of 1,002 patients transplanted from unrelated donors matched for age and background disease. The overall survival of patients who received stem cell transplants from a single locus mismatched family member was equivalent to that of patients who received BMTs from 6/6 HLA-matched unrelated donors for both standard-risk (acute leukemia in first or second complete remission, CML in first or second chronic phase, MDS without leukemic transformation) and high-risk diseases. The outcome following transplantation from a HLA single locus–mismatched family member was comparable to that following standard transplant from 6/6 HLA-matched unrelated donors. However, the availability of donors with a single locus mismatch remains low.

Haploidentical Stem Cell Transplantation of Purified CD34$^+$ Cells

A nationwide survey in Japan of the outcome of haploidentical transplants following negative T-cell depletion using the Isolex CD34$^+$ selection kit,[10] found 135 patients: 110 under age 16 and 25 older than 16. The indications for transplantation were 46 ALL, 32 acute nonlymphocytic leukemia (ANLL), 13 CML, 8 MDS, 6 neuroblastoma, 1 malignant leukemia (ML), 11 severe anaplastic anemia (SAA), 5 Fanconi's anemia, 2 inborn errors of metabolism, 6 severe combined immunodeficiency, 1 Wiskott-Aldrich syndrome, 3 hemophagocytic syndrome, and 1 chronic active Epstein-Barr virus infection. A total of 29 patients with standard-risk and 81 with high-risk malignancies had been grafted with CD34$^+$ cells purified from bone marrow cells (n = 38), granulocyte colony-stimulating factor (G-CSF)–mobilized peripheral blood (n = 74), or from a mixture of marrow and blood (n = 23) donated from HLA haploidentical family members. The status of HLA disparity between the recipients and the donors was: 0/6–1/6 mismatch: n = 28; 2/6 mismatch: n = 64; and 3/6 mismatch: n = 43. The removal rate of CD3$^+$ cells was log 3.3–3.9, and the concentration of CD34$^+$ cells after purification was 89.6%–93.6%, resulting in the following cell doses: 38 patients received 3.2 ± 2.3 × 10^6/kg CD34$^+$ cells derived from bone marrow, 74 patients received 5.5 ± 3.6 × 10^6/kg CD34$^+$ cells from peripheral blood, and 23 patients received 4.9 ± 7.1 × 10^6/kg CD34$^+$ cells from the mixture of bone marrow and peripheral blood. For prophylaxis of graft rejection and for GVHD, 47 of 135 received ATG and 105 patients received post-transplant GVHD prophylaxis with cyclosporine, tacrolimus, methotrexate, and corticosteroid, either alone or in combination. Nevertheless, in 30 transplants, CD34$^+$ cell selection was the only measure of GVHD prophylaxis. Among these T-cell negatively depleted single-haploidentical transplants from family members, the incidence of grade III–IV acute GVHD was 8.4%, close to that observed for transplants from HLA genotypically matched siblings or from 6/6 HLA-matched unrelated donors without T-cell depletion (Table 6). However,

Table 6 Probability of Acute GVHD According to Donor Type

Donor	Incidence of Grade III–IV Acute GVHD
Syngeneic (n = 85)	2.4%
HLA-matched sibling (n = 4,701)	8.1%
HLA-mismatched sibling (n = 294)	16.7%
HLA-matched unrelated (n = 1,379)	13.1%
HLA-mismatched unrelated (n = 991)	22.8%
HLA-matched relative other than sibling (n = 227)	11.0%
HLA-mismatched related other than sibling (n = 357)	17.9%

Data from JSHCT, December 2001.

the rate of engraftment (82%) was lower than that after transplant from unrelated donors (95%).[6] The observed overall survival of 27.4% and the DFS of 18.5% were insufficient when compared to those obtained from standard transplants (Tables 1 and 2) although most of the patients were transplanted at an advanced stage of disease.

Effect of HLA Allele Mismatches in Unrelated BMT Using Tacrolimus Prophylaxis

A prospective phase II study was performed to investigate the ability of tacrolimus to prevent GVHD after BMT from HLA allele-mismatched unrelated donors. Patients had either leukemia or MDS at various clinical stages, were between the ages of 16 and 50, and had a clinical performance status of 0 to 2. Tacrolimus was administered at a dose of 0.03 mg/kg by 24-hour continuous infusion from day 1 and converted to oral administration with appetite recovery. The dose of tacrolimus was adjusted to keep its blood concentration between 15 and 20 ng/mL. DFS was 70% for standard-risk patients (acute leukemia in first complete remission, CML in first chronic phase, and refractory anemia of MDS; n = 21) and 30% for high-risk patients (n = 31). The frequency of acute GVHD and DFS were compared with age- and disease-matched patients receiving cyclosporine and unrelated transplantation through the JMDP during the same time period (Table 7). The frequency of grades III–IV acute GVHD among patients who were transplanted from single-locus HLA class I allele mismatched donors with tacrolimus was 23.1%, which was much lower than that of the cyclosporine group (58.3%). For patients receiving marrow grafts from single-locus HLA class II allele mismatched donors, the frequency of grades III–IV acute GVHD in the tacrolimus group was 10.5% and that of the cyclosporine group, 16.1%, both of which were lower than that observed for single HLA class I allele mismatch transplants, and the difference between the two groups was small. This can be explained by our previous reports,[23,24] which showed that a single class II allele mismatch did not increase the frequency of severe acute GVHD in Japanese patients receiving cyclosporine-based GVHD prophylaxis. DFS of the patients transplanted from single-locus HLA class I mismatched unrelated donors with tacrolimus was equivalent to that of patients transplanted from single-locus HLA class II mismatched unrelated donors with either cyclosporine or tacrolimus.[25] Our previous reports confirmed that HLA class I allele mismatch but not class II allele mismatch was a significant risk factor for DFS of Japanese patients transplanted from unrelated donors receiving cyclosporine-based GVHD prophylaxis.[23,24] In the present study, tacrolimus improved the outcome of HLA class I mismatch transplants to the level of class II mismatch transplants. Tacrolimus may be more effective for HLA-mismatched transplants such as haploidentical transplants.

Haploidentical Transplantation With Tacrolimus But Without T-Cell Depletion From Related Donors Suspected to be Immunologically Tolerant to Recipients

The presence of microchimerism of noninherited maternal antigens (NIMA) in offspring as well as inherited paternal antigens (IPA) in the mothers of transplant recipients was examined.[26] NIMA or IPA microchimerism exists for more than 50 years in both offspring and mothers, suggesting that the offspring and mother might be immunologically tolerant of each other (Table 7). Preclinical trials of transplants between offspring who shared the paternal but not maternal HLA haplotype with donors who had NIMA microchimerism were performed using tacrolimus-based GVHD prophylaxis.[27] Patients' characteristics are described in Table 8, and the outcomes in Table 9. Engraftment was obtained in all patients. The probabilities of grades III–IV acute GVHD among patients who received stem cells from two- or three-antigen–mismatched donors were 24% and 29%, respectively, which was slightly higher than the overall frequency of grade III–IV acute GVHD in transplants from unrelated do-

Table 7 Probability of Grade III–IV Acute GVHD and DFS After HLA Allele-Mismatched Unrelated Donor BMT: Cyclosporine Versus Tacrolimus

	Probability of Grade III–IV Acute GVHD	3-Year DFS
Class 1 DNA 1 mismatch		
Cyclosporine (n = 12)	58%	25%
Tacrolimus (n = 13)	23%	52%
Class 2 DNA 1 mismatch		
Cyclosporine (n = 31)	16%	55%
Tacrolimus (n = 19)	10%	52%

Data from Nishida et al.[23]

Table 8 Incidence of Long-Term Fetomaternal Chimerism With Reference to Duration

Duration of Chimerism	Maternal Cell Chimerism in Offspring			Offspring Cell Chimerism in Mother		
	No. of Subjects	No. Detected	%	No. of Subjects	No. Detected	%
0–9	39	23	59	42	32	76
10–19	59	46	78	44	36	80
20–29	71	56	79	51	40	78
30–39	39	25	64	17	11	65
40–49	26	13	50	11	8	73
50–59	11	6	55	1	1	100
60–69	1	1	100	0	0	0
Total	246	170	69	166	127	77

NOTE. Represented by offspring's age at blood sampling.
Unpublished data from H. Saji, 2000.

nors (18.4%)[6] but equivalent to the frequency observed for transplants from class I mismatched unrelated donors (HLA -A/B one allele mismatch: 27.8%; HLA-C one allele mismatch: 20.6%).[24] The probability of survival for standard-risk patients was comparable for those with HLA genotypically matched sibling donors and those with HLA allele-matched unrelated donors (Table 10; see Tables 1 and 2).

Conclusion

HLA matching is an essential prerequisite for the success of HSCT from related[12,28] and unrelated[24,29] marrow donors, in part because it predicts GVHD, a significant factor for post-transplant survival. In transplantation of peripheral blood stem cells, GVHD may be more frequent than in marrow transplant[30,31] due to the high dose of T cells in the stem cell preparation. In CBSCT, where requirements of HLA matching are less stringent than for BMT or PBSCT, the outcome is still affected by disparity of HLA.[32,33] Another factor considered to be critical is the timing of transplant in relation to the patient's clinical course and the potential loss of the optimal moment for transplantation due to delays in identifying a suitable donor. Our results demonstrate that when a HLA suitably matched stem cell source cannot be identified among current donor pools, HLA-haploidentical relatives among family members may allow transplantation without delay. Retrospective analysis of transplants from HLA-mismatched siblings among Japanese patients[22] supports the usefulness of such alternative stem cell sources. Our experience shows that transplantation from HLA-haploidentical sibling donors predicted to be immunologically tolerant to the recipients produced survival equivalent to that obtained from transplantation using HLA-matched related or unrelated donors, when tacrolimus was employed for GVHD prophylaxis, without T-cell depletion. Efforts to achieve successful stem cell transplant beyond the conventional HLA barrier must be continued.

Table 9 Characteristics of Recipients

No.	33
Sex (M/F)	14/19
Median age, yr (range)	28 (2–57)
Diagnosis	
AML	10
ALL/LBL	12
CML	7
DLBCL	3
ATL	1
Risk status at HSCT*	
Intermediate	13
High	20

Abbreviations: LBL, lymphoblastic lymphoma; DLBCL, diffuse large B-cell lymphoma; ATL, adult T-cell leukemia.
Data from Ichinohe et al.[26]
*Risk status of hematological malignancies at the time of HSCT was defined as follows: Intermediate, advanced CR/PR/CP, chemosensitive relapse; High, primary refractory disease or chemoresistant relapse.

Acknowledgment

The studies reviewed here were supported in part by Health and Labor Sciences Research Grants, Research on Human Genome, Tissue Engineering, Ministry of Health, Labor and Welfare, Japan.

Table 10 Probability of Grade III–IV Acute GVHD and DFS After HLA-Haploidentical Related Transplantation

	Probability of	
	Grade III–IV Acute GVHD	DFS
In GVH direction		
HLA 2-antigen mismatch (n = 21)	24%	
HLA 3-antigen mismatch (n = 11)	29%	
Transplanted in remission (n = 13)		62%*
Transplanted in chemorefractory (n = 22)		22%†

Abbreviation: GVH, graft versus host.
Data from Ichinohe et al.[26]
*At 3 years.
†At 2.3 years.

References

1. Thomas ED: Karnofsky Memorial Lecture: Marrow transplantation for malignant disease. J Clin Oncol 1:517-531, 1983
2. Hirabayashin N, Kodera Y, Matsuyama T, Tanimoto M, Horibe K, Naoe T, et al: Bone marrow transplantation in 614 patients: Twenty years experience of Nagoya Bone Marrow Transplantation Group (NBMTG). Transplant Proc 27:1380-1382, 1995
3. Storb RI, Thomas ED, Buckner CD, Clift RA, Johnson FL, Fefer A, et al: Allogeneic marrow grafting for treatment of aplastic anemia. Blood 43:157-180, 1974
4. Kojima S, Matsuyama T, Kodera Y, Hirabayashi N, Morishima Y, Iwamura H, et al: Allogeneic bone marrow transplantation in 25 patients with severe aplastic anemia. Acta Haematol Jpn 51:705-714, 1988
5. Kernan NA, Bartsch G, Ash RC, Beatty PG, Champlin R, Filipovich A, et al: Analysis of 462 transplantations from unrelated donors facilitated by the National Marrow Donor Program. N Engl J Med 328:592-602, 1993
6. Kodera Y, Morishima Y, Kato S, Akiyama Y, Sao H, Matsuyama T, et al: Analysis of 500 bone marrow transplants from unrelated donors (UR-BMT) facilitated by the Japan Marrow Donor Program: Confirmation of UR-BMT as a standard therapy for patients with leukemia and aplastic anemia. Bone Marrow Transplant 24:995-1003, 1999
7. Deeg HJ, Seidel K, Casper J, Anasetti C, Davies S, Gajeweski JL, et al: Marrow transplantation from unrelated donors for patients with severe aplastic anemia who have failed immunosuppressive therapy. Biol Blood Marrow Transplant 5:243-252, 1999
8. Kojima S, Matsuyama T, Kato S, Kigasawa H, Kobayashi R, Kikuta A, et al: Outcome of 154 patients with severe aplastic anemia who received transplants from unrelated donors: The Japan Marrow Donor Program. Blood 100:799-803, 2002
9. Broxmyer HE: Human umbilical cord blood is a source of transplantable hematopoietic stem/progenitor cells. Proc Natl Acad Sci U S A 86:3828-3832, 1989
10. Kato S, Nishihira H, Hara K, Kato K, Takahashi T, Sato N, et al: Cord blood transplantation and cord blood bank in Japan. Bone Marrow Transplant 25:S68-S70, 2000 (suppl 2)
11. Hansen JA, Beatty PG, Anasetti C, Clift RA, Martin PJ, Sanders J, et al: Treatment of leukemia by marrow transplantation from donors other than HLA genotypically identical siblings, in Gale RP, Champlin RE (eds): Progress in Bone Marrow Transplantation. New York, NY, Liss, 1987, pp 667-676
12. Horibe K, Yoshida J, Oiwa K, Kodera Y, Iwamura H, Matsuyama T, et al: Bone marrow transplantation from related donors other than HLA identical siblings in Japanese patients with hematological malignancies. Acta Haematol Jpn 53:94-102, 1990
13. Gorin NC, Lopez M, Laporte JP, Quittet P, Lesage S, Lemoine F, et al: Preparation and successful engraftment of purified CD-34$^+$ bone marrow progenitor cells in patients with non-Hodgkin's lymphoma. Blood 85:1647-1654, 1995
14. Kato S, Yabe H, Yasui M, Kawa K, Yoshida T, Watanabe A, et al: Allogeneic hematopoietic transplantation of CD34$^+$ selected cells from an HLA haplo-identical related donor. A long-term follow-up of 135 patients and a comparison of stem cell source between the bone marrow and the peripheral blood. Bone Marrow Transplant 26:1281-1290, 2000
15. Hiraoka A, Ohashi Y, Okamoto S, Moriyama Y, Nagao T, Kodera Y, et al: Phase III study comparing tacrolimus (FK506) with cyclosporine for graft-versus-host disease prophylaxis after allogeneic bone marrow transplantation. Bone Marrow Transplant 28:181-185, 2001
16. van Rood JJ, Loberiza FR, Jr, Zhang MJ, Oudshoorn M, Claas F, Cairo MS, et al: Effect of tolerance to noninherited maternal antigens on the occurrence of graft-versus-host disease after bone marrow transplantation from a parent or an HLA haploidentical sibling. Blood 99:1572-1577, 2002
17. Tamaki S, Ichinohe T, Matsuo K, Hamajima N, Hirabayashi N, Dohy H: Japan Society of Hematopoietic Cell Transplantation: Superior survival of blood and marrow stem cell recipients given maternal grafts over recipients given paternal grafts. Bone Marrow Transplant 28:375-380, 2001
18. The Japan Society for Hematopoietic Cell Transplantation Office of Nationwide Survey: The Japan Society for Hematopoietic Cell Transplantation. Annual Report of Nationwide Survey 2004 (in Japanese). Nagoya, Japan, 2004
19. Morishima Y, Kodera Y, Hirabayashi N, Tanimoto M, Matsuyama T, Horibe K, et al: Low incidence of acute GVHD in patients transplanted with marrow from HLA-A, B, DR-compatible unrelated donors among Japanese. Bone Marrow Transplant 15:235-239, 1995
20. Morishima Y, Morishita Y, Tanimoto M, Ohno R, Saito H, Horibe K, et al: Low incidence of acute graft graft-versus-host disease by the administration of methotrexate and cyclosporine in Japanese leukemia patients after bone marrow transplantation from human leukocyte antigen compatible siblings: Possible role of genetic homogeneity. Blood 74:2252-2256, 1989
21. Beatty PG, Clift RA, Mickelson EM, Nisperos BB, Flournoy N, Martin PJ, et al: Marrow transplantation from related donors other than HLA HLA-identical siblings. N Engl J Med 313:765-771, 1985
22. Kanda Y, Chiba S, Hirai H, Sakamaki H, Iseki T, Kodera Y, et al: Allogeneic hematopoietic stem cell transplantation from family members other than HLA-identical siblings over the last decade (1991-2000). Blood 102:1541-1547, 2003
23. Sasazuki T, Juji T, Morishima Y, Kinukawa N, Kashiwabara H, Kodera Y, et al: Importance of HLA class I allele matching for clinical outcome after unrelated donor hematopoietic stem cell transplantation. N Engl J Med 339:1177-1185, 1998
24. Morishima Y, Sasazuki T, Inoko H, Juji T, Akaza T, Yamamoto K, et al: The clinical significance of human leukocyte antigen (HLA) allele compatibility in patients receiving a marrow transplant from serologically HLA-A, HLA-B, and HLA-DR matched unrelated donors. Blood 99: 4200-4206, 2002
25. Nishida T, Murayama T, Hirai H, Okamoto S, Sao H, Hara M, et al: Phase-2 study of FK506 for GVHD prophylaxis after BMT from HLA DNA typing mismatched unrelated donor. Rinshoketsueki 44:678, 2003 (in Japanese)
26. Ichinohe T, Maruya E, Saji H: Long-term feto-maternal microkimerism. Nature's hidden clue for alternative donor hematopoietic cell transplantation? Int J Hematol 76:229-237, 2002
27. Ichinohe T, Uchiyama T, Shimazaki S, Matsuo K, Tamaki S, Hino M, et al: Feasibility of HLA-haploidentical hematopoietic stem cell transplantation between noninherited maternal antigen (NIMA)-mismatched family members linked with long-term fetomaternal microkimerism. Blood 104:3821-3828, 2004
28. Beatty PG, Clift RA, Mickelson EM, Nisperos BB, Flournoy N, Martin PJ, et al: Marrow transplantation from related donors other than HLA-identical siblings. N Engl J Med 313:765-771, 1985
29. Petersdorf EW, Longton GM, Anasetti C, Martin PJ, Mickelson EM, Smith AG, et al. The significance of HLA-DRB1 matching on clinical outcome after HLA-A,B, DR identical unrelated donor marrow transplantation. Blood 86:1606-1613, 1995
30. Schmitz N, Bacigalupo A, Hasenclever D, Nagler A, Gluckman E, Clark P, et al: Allogeneic bone marrow transplantation vs filgrastim-mobilised peripheral blood progenitor cell transplantation in patients with early leukemia: First results of a randomised multicentre trial of European Group for Blood and Marrow Transplantation. Bone Marrow Transplant 21:995-1003, 1998
31. Harada M, Shinagawa K, Kawano T, Kasai M, Sawada H, Nakao S, et al: Allogeneic peripheral blood stem cell transplantation for standard-risk leukemia. A multicenter pilot study: Japanese experience. Japan Blood Cell Transplantation Study Group. Bone Marrow Transplant 21:s54-s56, 1998 (suppl 3)
32. Gluckman E, Rocha V, Arcese W, Michel G, Sanz G, Chan KW, et al: Factors associated with outcomes of unrelated cord blood transplant: Guidelines for donor choice. Exp Hematol 32:397-407, 2004
33. Nishihira H, Kato K, Isoyama K, Takahashi TA, Kai S, Kato S, et al: The Japanese Cord Blood Bank Network experience with cord blood transplantation from unrelated donors for haematological malignancies: An evaluation of graft-versus-host disease prophylaxis. Br J Haematol 120: 516-522, 2003

International Journal of
HEMATOLOGY

Current Status of Hematopoietic Cell Transplantation for Adult Patients with Hematologic Diseases and Solid Tumors in Japan

Masahiro Imamura,[a] Shigetaka Asano,[b] Mine Harada,[c] Yasuo Ikeda,[d] Koji Kato,[e] Shunichi Kato,[f] Keisei Kawa,[g] Seiji Kojima,[h] Yasuo Morishima,[i] Yoshihisa Morishita,[j] Tatsutoshi Nakahata,[k] Jun Okamura,[l] Shinichiro Okamoto,[d] Shintaro Shiobara,[m] Mitsune Tanimoto,[n] Masahiro Tsuchida,[o] Yoshiko Atsuta,[p] Kazuhito Yamamoto,[i] Junji Tanaka,[a] Nobuyuki Hamajima,[p] Yoshihisa Kodera[q]

[a]Department of Hematology and Oncology, Hokkaido University Graduate School of Medicine, Sapporo; [b]Consolidated Research Institute for Advanced Science and Medical Care, Waseda University, Tokyo; [c]Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medicine, Fukuoka; [d]Division of Hematology, Department of Internal Medicine, Keio University School of Medicine, Tokyo; [e]Division of Hematology and Oncology, Children's Medical Center, Red Cross Nagoya First Hospital, Nagoya; [f]Department of Cell Transplantation and Regenerative Medicine, Tokai University School of Medicine, Kanagawa; [g]Department of Pediatrics, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka; [h]Department of Pediatrics and Developmental Pediatrics, Nagoya University Graduate School of Medicine, Nagoya; [i]Department of Hematology and Cell Therapy, Aichi Cancer Center Hospital, Nagoya; [j]Department of Hematology and Oncology, JA Aichi Showa Hospital, Aichi; [k]Department of Pediatrics, Graduate School of Medicine, Kyoto University, Kyoto; [l]Institute for Clinical Research, National Kyushu Cancer Center, Fukuoka; [m]Department of Cellular Transplantation Biology, Kanazawa University Graduate School of Medicine, Kanazawa; [n]Department of Hematology and Oncology, Okayama University Graduate School of Medicine and Dentistry, Okayama; [o]Department of Pediatrics, Ibaragi Children's Hospital, Ibaragi; [p]Department of Preventive Medicine/Biostatistics and Medical Decision Making, Nagoya University Graduate School of Medicine, Nagoya; [q]Department of Hematology, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan

Received September 5, 2005; received in revised form November 10, 2005; accepted November 16, 2005

Abstract

A nationwide survey of hematopoietic cell transplantation (HCT) was started in Japan in 1991, and the analyzed survey data have been presented as the annual report of the Japan Society for Hematopoietic Cell Transplantation. The 10-year overall survival (OS) rates after HCT for each disease are as follows: acute myelogenous leukemia, 44.2%; acute lymphocytic leukemia, 33.7%; adult T-cell leukemia, 24.6%; chronic myelogenous leukemia, 53.3%; myelodysplastic syndrome, 37.3%; non-Hodgkin's lymphoma, 41.5%; Hodgkin's lymphoma, 50.8%; aplastic anemia, 72.5%; breast cancer, 37.1%; germ cell tumor, 52.6%; and ovarian cancer, 44.2%. The 5-year OS rates for multiple myeloma and lung cancer were 40.6% and 23.6%, respectively. Except in cord blood transplantation, engraftment was accomplished in more than 90% of patients. The respective frequencies of acute graft-versus-host disease (GVHD) and chronic GVHD were 41.1% and 34.9% for related bone marrow transplantation (BMT), 66.8% and 34.5% for unrelated BMT, 52.9% and 36.0% for allogeneic peripheral blood stem cell transplantation, and 53.3% and 32.1% for allogeneic cord blood transplantation. OS for each disease was analyzed by patient age, stem cell source, donor type, disease status, and disease type. These data provide objective and valuable information for hematologists as well as for patients who need HCT.
Int J Hematol. 2006;83:164-178. doi: 10.1532/IJH97.05134

Key words: Hematopoietic cell transplantation; Overall survival; Hematologic malignancies; Solid tumors; Graft-versus-host disease

1. Introduction

Hematopoietic cell transplantation (HCT) is a powerful treatment modality for various hematologic diseases [1,2]. On some occasions, HCT is also used for certain solid tumors, such as breast cancer, ovarian cancer, and germ cell tumors, although there is still a limitation in obtaining improved survival rates [3]. HCT comprises autologous HCT (auto-HCT) and allogeneic HCT (allo-HCT). Recently, auto-HCT has mainly been performed with peripheral blood stem cells (PBSC) rather than with bone marrow stem cells (BMSC) [4]. There are many types of allo-HCT, including transplantation with related or unrelated BMSC, with related or unrelated PBSC, and with

Correspondence and reprint requests: Masahiro Imamura, MD, Department of Hematology and Oncology, Hokkaido University Graduate School of Medicine, Kita-15, Nishi-7, Kita-ku, Sapporo, Japan 060-8638; 81-11-706-7213; fax: 81-11-706-7823 (e-mail: mimamura@med.hokudai.ac.jp).

related or unrelated cord blood stem cells (CBSC). Furthermore, nonmyeloablative HCT has recently been introduced into the clinics in addition to myeloablative HCT [5]. The current availability of various kinds of stem cell sources, donors, and conditioning regimens thus complicates the choice of an appropriate HCT procedure for each patient. The frequency of HCT with related CBSC is very low. Furthermore, we cannot use unrelated allo-PBSC in Japan, because their use has not yet been approved by the Ministry of Health, Labour and Welfare of Japan. A nationwide survey on adult HCT by the Japan Society for Hematopoietic Cell Transplantation (JSHCT) began in 1993. Registration of transplantations, including those from the Japan Marrow Donor Program (JMDP), has been ongoing since 1991, and an annual report has been published every year. Because the annual report provides information on the current status of HCT in Japan, this report has become very important to hematologists specializing in HCT and patients with hematologic diseases for determining the type of donor, the type of hematopoietic stem cells, the timing of HCT, and the type of HCT. Although a randomized trial has to be performed to determine the specific treatments for obtaining reliable results in problematic patients, the nationwide HCT survey by retrospective analysis has become somewhat useful, because it is capable of publishing several informative reports [6-8]. In the present report, we conducted a comprehensive analysis of overall survival (OS) of adult patients with hematologic diseases or solid tumors after auto-HCT or allo-HCT according to patient age, stem cell source, donor type, disease status, and disease type to clarify the current status of HCT in Japan.

2. Patients and Methods

2.1. Analyzed Population

We analyzed the cases of 14,255 adult patients older than 16 years who underwent auto-HCT, related allogeneic bone marrow transplantation (related BMT), related allogeneic PBSC transplantation (related allo-PBSCT), unrelated allogeneic BMT (unrelated BMT), and unrelated allogeneic cord blood transplantation (unrelated allo-CBT) between January 1991 and December 2002. These cases were all first transplantations, and repeatedly registered cases were omitted. Numbers of patients and their median ages were 5488 and 47 years (range, 16-91 years) for auto-HCT, 3746 and 35 years (range, 16-69 years) for related BMT, 3133 and 32 years (range, 16-66 years) for unrelated BMT, 1413 and 44 years (range, 16-85 years) for allo-PBSCT, 156 and 38 years (range, 16-72 years) for allo-CBT, and 319 and 44 years (range, 16-73 years) for others (Table 1). The last category (n = 319) consists of patients whose transplanted stem cells or the donor were not entered on the report form. Male-female ratios were 3058:2425 for auto-HCT, 2273:1472 for related BMT, 1924:1206 for unrelated BMT, 843:565 for allo-PBSCT, 70:84 for allo-CBT, and 198:120 for others.

Because allo-PBSCT and allo-CBT cases in Japan mostly consist of related allo-PBSCT and unrelated allo-CBT, we prefer to use the terms *allo-PBSCT* and *allo-CBT* instead of *related allo-PBSCT* and *unrelated allo-CBT*. The data for the 14,255 patients were from 11,159 patients registered in the nationwide survey of the JSHCT and from 3096 patients reported to the JMDP. The sudden decrease in 2000 in the frequency of BMT, which had been increasing until 1998, coincided with an increase in the frequency of allo-PBSCT. This dramatic change is mainly due to the approval of insurance coverage for allo-PBSCT in Japan, which occurred in 2000. Furthermore, the increasing frequency of allo-CBT since 2000 has been dependent on the increase in storage capacity for cord blood.

The numbers of patients with each disease were as follows: acute myelogenous leukemia (AML), 2966; acute lymphocytic leukemia (ALL), 1975; adult T-cell leukemia (ATL), 108; chronic myelogenous leukemia (CML), 2027; myelodysplastic syndrome (MDS), 979; other leukemias, 127; non-Hodgkin's lymphoma (NHL), 3339; Hodgkin's lymphoma (HL), 276; multiple myeloma (MM), 653; aplastic anemia (AA), 448; paroxysmal nocturnal hemoglobinuria, 10; myelofibrosis, 12; solid tumors, 1200; and other diseases, 48. Patients with NHL, HL, MM, and solid tumors were treated mainly with auto-HCT. Cases of solid tumors comprised patients with breast cancer (n = 424), germ cell tumor (n = 261), lung cancer (n = 114), and ovarian cancer (n = 161).

2.2. Transplantations by Disease Type

The AML patients (n = 2966) received 524 auto-HCT, 1069 related BMT, 868 unrelated BMT, 380 allo-PBSCT, 52 allo-CBT, and 73 others (Table 1). The ALL patients (n = 1975) received 252 auto-HCT, 739 related BMT, 695 unrelated BMT, 211 allo-PBSCT, 32 allo-CBT, and 46 others. The ATL patients (n = 108) received 18 auto-HCT, 22 related BMT, 13 unrelated BMT, 46 allo-PBSCT, 4 allo-CBT, and 5 others. The CML patients (n = 2027) received 25 auto-HCT, 890 related BMT, 858 unrelated BMT, 191 allo-PBSCT, 18 allo-CBT, and 45 others. The MDS patients (n = 979) received 16 auto-HCT, 385 related BMT, 323 unrelated BMT, 186 allo-PBSCT, 33 allo-CBT, and 36 others. The patients with other leukemias (n = 127) received 15 auto-HCT, 56 related BMT, 13 unrelated BMT, 39 allo-PBSCT, 3 allo-CBT, and 1 other. The NHL patients (n = 3339) received 2663 auto-HCT, 236 related BMT, 148 unrelated BMT, 208 allo-PBSCT, 11 allo-CBT, and 73 others. The HL patients (n = 276) received 265 auto-HCT, 9 related BMT, 1 allo-PBSCT, and 1 other. The MM patients (n = 653) received 549 auto-HCT, 52 related BMT, 7 unrelated BMT, 32 allo-PBSCT, and 13 others. The AA patients (n = 448) received 264 related BMT, 129 unrelated BMT, 44 allo-PBSCT, 2 allo-CBT, and 9 others. The patients with paroxysmal nocturnal hemoglobinuria (n = 10) received 6 related BMT, 3 allo-PBSCT, and 1 other. The myelofibrosis patients (n = 12) received 8 related BMT, 2 unrelated BMT, and 2 allo-PBSCT. The patients with solid tumors (n = 1200) received 1122 auto-HCT, 6 related BMT, 2 unrelated BMT, 56 allo-PBSCT, and 14 others. The patients with other diseases (n = 48) received 27

Table 1.
Patient Characteristics*

Characteristic	Autologous HCT	Related BMT	Unrelated BMT	Allogeneic PBSCT	Allogeneic CBT	Others	Total
Patients, n	5488	3746	3133	1413	156	319	14,255
Median age (range), y	47 (16-91)	35 (16-69)	32 (16-66)	44 (16-85)	38 (16-72)	44 (16-73)	39 (16-91)
M/F sex, n	3058/2425	2273/1472	1924/1206	843/565	70/84	198/120	8366/5872
Primary disease, n (%)							
AML	524 (9.5)	1069 (28.5)	868 (27.2)	380 (26.9)	52 (33.3)	73 (22.9)	2966 (20.8)
ALL	252 (4.6)	739 (19.7)	695 (22.2)	211 (14.9)	32 (20.5)	45 (14.4)	1975 (13.9)
ATL	18 (0.3)	22 (0.6)	13 (0.4)	46 (3.3)	4 (2.6)	5 (1.6)	108 (0.8)
CML	25 (0.5)	890 (23.8)	858 (27.4)	191 (13.5)	18 (11.5)	45 (14.1)	2027 (14.2)
Other leukemia	15 (0.3)	56 (1.5)	13 (0.4)	39 (2.8)	3 (1.9)	1 (0.3)	127 (0.9)
MDS	16 (0.3)	385 (10.3)	323 (10.3)	186 (13.2)	33 (21.2)	36 (11.3)	979 (6.9)
AA	0 (0.0)	264 (7.0)	129 (4.1)	44 (3.1)	2 (1.3)	9 (2.8)	448 (3.1)
PNH	0 (0.0)	6 (0.2)	0 (0.0)	3 (0.2)	0 (0.0)	1 (0.3)	10 (0.1)
MF	0 (0.0)	8 (0.2)	2 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	12 (0.1)
NHL	2663 (48.5)	236 (6.3)	148 (4.7)	208 (14.7)	11 (7.1)	73 (22.9)	3339 (23.4)
HL	265 (4.8)	9 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.3)	276 (1.9)
MM	549 (10.0)	52 (1.4)	7 (0.2)	32 (2.3)	0 (0.0)	13 (4.1)	653 (4.1)
Solid tumors	1122 (20.4)	6 (0.2)	2 (0.1)	56 (4.0)	0 (0.0)	14 (4.4)	1200 (8.4)
Other diseases	27 (0.5)	2 (0.1)	14 (0.4)	4 (0.3)	0 (0.0)	1 (0.3)	48 (0.3)
Unknown/not reported	11 (0.2)	2 (0.1)	61 (1.9)	10 (0.7)	1 (0.6)	1 (0.3)	86 (0.6)
Disease status, n (%)							
1CR or 1CP	1526 (35.1)	1845 (53.3)	1216 (41.5)	423 (32.7)	25 (16.3)	88 (30.0)	5123 (41.0)
All others	2822 (64.9)	1614 (46.7)	1717 (58.5)	871 (67.3)	128 (83.7)	205 (70.0)	7357 (59.0)
HLA matching, n (%)							
A, B, DR match		3253 (92.6)	1587 (62.5)	723 (86.5)	1 (1.8)	103 (79.8)	5668 (80.1)
A, B, DR mismatch		261 (7.4)	952 (37.5)	113 (13.5)	56 (98.2)	26 (20.2)	1408 (19.9)
Conditioning regimen, n (%)							
TBI + CY ± other drugs	247 (5.3)	1848 (51.0)	2255 (72.8)	538 (42.9)	110 (75.3)	116 (53.2)	5114 (39.3)
TBI ± other drugs	195 (4.2)	427 (11.8)	233 (7.5)	112 (8.9)	18 (12.3)	19 (8.7)	1004 (7.7)
BU + CY ± other drugs	335 (7.2)	953 (26.3)	461 (14.9)	159 (12.7)	2 (1.4)	32 (14.7)	1942 (14.9)
CY ± other drugs	2287 (49.1)	259 (7.2)	58 (1.9)	34 (2.7)	2 (1.4)	16 (7.3)	2656 (20.4)
FL (CL) ± other drugs ± TBI	0 (0.0)	46 (1.3)	62 (2.0)	391 (31.2)	12 (8.2)	26 (11.9)	537 (4.1)
Other regimen	1596 (34.2)	88 (2.4)	30 (1.0)	21 (1.7)	1 (1.4)	9 (4.1)	1746 (13.4)
GVHD prophylaxis, n (%)							
CyA ± MTX	0 (0.0)	3376 (91.4)	1978 (64.1)	1190 (85.9)	122 (79.7)	163 (74.1)	6833 (48.7)
FK506 ± MTX	0 (0.0)	239 (6.5)	1093 (35.4)	164 (11.8)	25 (16.3)	41 (18.6)	1563 (11.1)
Others	0 (0.0)	49 (1.3)	16 (0.5)	18 (1.3)	5 (3.3)	10 (4.5)	101 (0.7)
None	5488 (100)	28 (0.8)	0 (0.0)	14 (1.0)	1 (0.7)	6 (2.7)	5537 (39.5)

*HCT indicates hematopoietic cell transplantation; BMT, bone marrow transplantation; PBSCT, peripheral blood stem cell transplantation; CBT, cord blood transplantation; AML, acute myelogenous leukemia; ALL, acute lymphocytic leukemia; ATL, adult T-cell leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; AA, aplastic anemia; PNH, paroxysmal nocturnal hemoglobinuria; MF, myelofibrosis; NHL, non-Hodgkin's lymphoma; HL, Hodgkin's lymphoma; MM, multiple myeloma; 1CR, first complete remission; 1CP, first chronic phase; TBI, total body irradiation; CY, cyclophosphamide; BU, busulfan; FL, fludarabine; CL, cladribine; GVHD, graft-versus-host disease; CyA, cyclosporin A; MTX, methotrexate; FK506, tacrolimus.

auto-HCT, 2 related allo-BMT, 14 unrelated BMT, 4 allo-PBSCT, and 1 other. The diagnoses of 86 patients were not reported.

2.3. Disease Status at Transplantation

The 5123 patients who underwent transplantation in the first complete remission (1CR) or the first chronic phase (1CP) received 1526 auto-HCT, 1845 related BMT, 1216 unrelated BMT, 423 allo-PBSCT, 25 allo-CBT, and 88 others (Table 1). In contrast, the 7357 patients who underwent transplantation at stages other than 1CR or 1CP received 2822 auto-HCT, 1614 related BMT, 1717 unrelated BMT, 87 allo-PBSCT, 128 allo-CBT, and 205 others.

2.4. HLA-Matching Grade in Donor and Host

A serologic typing match for HLA-A, HLA-B, and HLA-DR between the donor and the host was present for 5668 patients (Table 1), and these patients received related BMT (n = 3253), unrelated BMT (n = 1587), allo-PBSCT (n = 723), allo-CBT (n = 1), and others (n = 103). A serologic typing mismatch in HLA-A, HLA-B, or HLA-DR between the donor and the host was present for 1408 patients, and these patients underwent related BMT (n = 261), unrelated BMT (n = 952), allo-PBSCT (n = 113), allo-CBT (n = 56), and others (n = 26). DNA typing for HLA-A, HLA-B, and HLA-DR was not introduced by the JMDP until 1997; therefore, the analysis of patients from January 1991 to December 2002 was made by using the data from serologic typing.

2.5. Conditioning Regimen for Transplantation

Total body irradiation (TBI) and cyclophosphamide with or without other drugs was used in 247 auto-HCT, 1848 related BMT, 2255 unrelated BMT, 538 allo-PBSCT, 110 allo-CBT, and 116 others (Table 1). TBI with or without other drugs was used in 195 auto-HCT, 427 related BMT, 233 unrelated BMT, 112 allo-PBSCT, 18 allo-CBT, and 19 others. Busulfan and cyclophosphamide with or without other drugs was used in 335 auto-HCT, 953 related BMT, 461 unrelated BMT, 159 allo-PBSCT, 2 allo-CBT, and 32 others. Cyclophosphamide with or without other drugs was used in 2287 auto-HCT, 259 related BMT, 58 unrelated BMT, 34 allo-PBSCT, 2 allo-CBT, and 16 others. Fludarabine or cladribine (± other drugs ± TBI) was used in 46 related BMT, 62 unrelated BMT, 391 allo-PBSCT, 12 allo-CBT, and 26 others. In allo-PBSCT cases, a regimen of fludarabine or cladribine (± other drugs ± TBI) was frequently used, suggesting the increasing use of nonmyeloablative stem cell transplantation with reduced-intensity conditioning regimens. Other regimens were used in 1596 auto-HCT, 88 related BMT, 30 unrelated BMT, 21 allo-PBSCT, 1 allo-CBT, and 9 others.

2.6. Graft-versus-Host Disease Prophylaxis

Cyclosporin A prophylaxis for graft-versus-host disease (GVHD) was used with or without short-term methotrexate treatment in 3376 related BMT, 1978 unrelated BMT, 1190 allo-PBSCT, 122 allo-CBT, and 163 others (Table 1). FK506 (tacrolimus) prophylaxis with or without short-term methotrexate treatment was used in 239 related BMT, 1093 unrelated BMT, 164 allo-PBSCT, 25 allo-CBT, and 41 others. Other prophylactic regimens were used in 49 related BMT, 16 unrelated BMT, 18 allo-PBSCT, 5 allo-CBT, and 10 others. No prophylaxis was used in 5488 auto-HCT, 28 related BMT, 14 allo-PBSCT, 1 allo-CBT, and 6 others.

2.7. Statistical Analysis

OS was defined as the duration between the date of transplantation and the date of death or last follow-up, whichever came first. For survival analyses, OS curves were estimated by the Kaplan-Meier product-limit method, and differences in survival were assessed by the log-rank test. Because the analysis of all of the data was exploratory, 2-sample tests were performed without adjusting for multiple comparisons, even when 3 or more groups were compared. All of the statistical analyses were conducted with the Stata software package (version 8; StataCorp, College Station, TX, USA).

3. Results

3.1. Frequency of Engraftment and GVHD

Engraftment was obtained in more than 90% of patients, except in those who underwent allo-CBT (Table 2). The frequencies of acute GVHD were as follows: 26.8% grade I, 16.1% grade II, 5.4% grade III, and 2.8% grade IV in related BMT; 27.2% grade I, 23.7% grade II, 9.1% grade III, and 6.8% grade IV in unrelated BMT; 14.6% grade I, 21.7% grade II, 10.7% grade III, and 5.9% grade IV in allo-PBSCT; 25.0% grade I, 21.2% grade II, 4.5% grade III, and 2.6% grade IV in allo-CBT; and 9.4% grade I, 19.7% grade II, 9.1% grade III, and 3.1% grade IV in others. Chronic GVHD was observed in 34.9% of related BMT, 34.5% of unrelated BMT, 36.0% of allo-PBSCT, 32.1% of allo-CBT, and 24.1% of others.

3.2. OS for Each Disease

The 10-year OS rate for each disease was 44.2% in AML (n = 2966), 33.7% in ALL (n = 1975), 24.6% in ATL (n = 108), 53.3% in CML (n = 2027), 37.3% in MDS (n = 979), 41.5% in NHL (n = 3339), 50.8% in HL (n = 276), 72.5% in AA (n = 448), 37.1% in breast cancer (n = 424), 52.6% in germ cell tumor (n = 261), and 40.6% in ovarian cancer (n = 161). The 5-year OS rates in MM (n = 653) and lung cancer (n = 114) were 40.6% and 23.6%, respectively. Auto-HCT was performed in only 17.7% of AML, 11.1% of ALL, 16.7% of ATL, 1.2% of CML, 1.6% of MDS, and 0% of AA, whereas it was performed in 79.8% of NHL, 96.0% of HL, 84.1% of MM, and 93.5% of solid tumors.

3.3. OS in Patients with AML

OS rates for auto-HCT and allo-HCT are shown in Table 3. Decreasing OS rate with increasing patient age was evident in both auto-HCT and allo-HCT. Interestingly, there was an approximately 10% difference in OS rate

Table 2.
Engraftment and Graft-versus-Host Disease (GVHD) Occurrence in Patients after Autologous or Allogeneic Transplantation*

	Autologous HCT, n (%)	Related BMT, n (%)	Unrelated BMT, n (%)	Allogeneic PBSCT, n (%)	Allogeneic CBT, n (%)	Others, n (%)
Engraftment	5321/5488 (97.0)	3553/3746 (94.8)	2855/3133 (91.1)	1301/1413 (92.1)	106/156 (67.9)	290/319 (90.9)
Acute GVHD						
0		1622/3746 (43.3)	831/3133 (26.5)	542/1413 (38.4)	34/156 (21.8)	60/319 (18.8)
I		1003/3746 (26.8)	853/3133 (27.2)	206/1413 (14.6)	39/156 (25.0)	30/319 (9.4)
II		602/3746 (16.1)	743/3133 (23.7)	306/1413 (21.7)	33/156 (21.2)	63/319 (19.7)
III		202/3746 (5.4)	285/3133 (9.1)	151/1413 (10.7)	7/156 (4.5)	29/319 (9.1)
IV		106/3746 (2.8)	214/3133 (6.8)	83/1413 (5.9)	4/156 (2.6)	10/319 (3.1)
Chronic GVHD		1309/3746 (34.9)	1080/3133 (34.5)	509/1413 (36.0)	50/156 (32.1)	77/319 (24.1)

*HCT indicates hematopoietic cell transplantation; BMT, bone marrow transplantation; PBSCT, peripheral blood stem cell transplantation; CBT, cord blood transplantation.

Table 3.
Survival Rates in Acute Myelogenous Leukemia Patients Who Received Autologous or Allogeneic Transplants*

	Autologous Transplantation		Allogeneic Transplantation		
Age Range, y	Time after Transplantation, y	Survival Rate, % (n)	Time after Transplantation, y	Survival Rate, % (n)	*P*
16-19	10	60.7 (30)	10	52.7 (223)	.5335
20-29	10	64.4 (98)	10	51.3 (612)	.0111
30-39	10	53.0 (103)	10	40.6 (636)	.0592
40-49	10	47.8 (114)	10	38.8 (613)	.0128
50-59	10	39.8 (128)	10	31.2 (248)	<.0001
60-69	5	33.7 (46)	5	32.5 (27)	.3559

*Numbers of cases are indicated in parentheses.

between auto-HCT and allo-HCT patients, indicating that auto-HCT is superior to allo-HCT in patients younger than 60 years, although there was only a trend toward statistical significance ($P = .0592$) for patients between 30 and 39 years.

According to the analysis of OS by remission status, the best survival rate for auto-HCT occurred in the 1CR, followed by the 2CR, the 3CR, and non-CR (NCR) (1CR versus 2CR, $P = .0071$; 1CR versus 3CR, $P < .001$; 1CR versus NCR, $P < .0001$; 2CR versus 3CR, $P = .0139$; 3CR versus NCR, $P = .058$) (Figure 1A). In contrast, related BMT showed superior survival rates in the 1CR, as well as in the 2CR and even the 3CR (1CR versus 2CR, $P = .0971$; 1CR versus 3CR, $P = .0092$; 1CR versus NCR, $P < .0001$; 1CR versus 3CR, $P = .0092$; 2CR versus 3CR, $P = .0795$; 2CR versus NCR, $P < .0001$; 3CR versus NCR, $P = .0585$) (Figure 1B). In unrelated BMT, superior OS were observed in the 1CR and the 2CR, followed by the 3CR and NCR (1CR versus 2CR, $P = .2542$; 1CR versus 3CR, $P = .0041$; 1CR versus NCR, $P < .001$; 2CR versus 3CR, $P = .0507$; 2CR versus NCR, $P < .0001$; 3CR versus NCR, $P < .0002$) (Figure 1C). These results indicate that the timing of HCT is an important factor in gaining favorable survival rates. Interestingly, OS in allo-PBSCT in the 1CR was almost the same as that in the 2CR and the 3CR, but not in NCR (1CR versus 2CR, $P = .7436$; 1CR versus 3CR, $P = .3975$; 1CR versus NCR, $P < .0001$; 2CR versus 3CR, $P = .4787$; 2CR versus NCR, $P < .0001$; 3CR versus NCR, $P = .0903$) (Figure 1D).

OS by French-American-British (FAB) subtype are shown in Figure 2. The highest OS was observed in M3 in auto-HCT and allo-HCT, followed by M4, M2, M1, M0, and M5. The order in OS for related BMT was M3, M1, M2, M4, M5, M0, and M7. For unrelated BMT, a statistically significant difference occurred only between OS in M4 and OS in M7. In general, there are 3 FAB subtype groups in terms of OS: low risk (M3), intermediate risk (M1, M2, M4, and M5), and high risk (M0 and M7). The order in OS for allo-PBSCT was M3, M0, M2, M5, M4, M6, M1, and M7, although very similar OS were observed for all of the groups except M7. Because there are still few cases of the M6 and M7 subtypes and because the follow-up times were not long enough in some cases, OS for these types was difficult to analyze in a meaningful way.

The 5-year OS rates after related BMT (n = 1069), unrelated BMT (n = 868), and allo-PBSCT (n = 380) were 51.7%, 42.3%, and 41.6%, respectively. Fifty-two patients who received allo-CBT and underwent follow-up for 1 year showed an OS rate of 38.7%. There were statistically significant differences between allo-CBT and related BMT ($P < .0001$), between allo-CBT and unrelated BMT ($P = .0007$), between allo-CBT and allo-PBSCT ($P = .0002$), between related BMT and allo-PBSCT ($P = .0042$), and between related BMT and unrelated BMT ($P < .0001$). Although the follow-up times were short, OS in allo-CBT was inferior to that in other HCT, and OS of related BMT was superior to that in other HCT.

3.4. OS in Patients with ALL

OS rates in auto-HCT and allo-HCT decreased with age, although the OS rate in allo-HCT was superior to that in auto-HCT (Table 4). There were 3 patient age groups in terms of OS: good (16-29 years), intermediate (30-49 years), and poor (50-69 years).

OS in auto-HCT in the 1CR was superior to OS in the 2CR, the 3CR, and NCR (1CR versus 2CR, $P < .0001$; 1CR versus 3CR, $P = .1567$; 1CR versus NCR, $P < .0001$; 2CR versus 3CR, $P = .4645$; 2CR versus NCR, $P = .0004$; 3CR versus NCR, $P = .0234$) (Figure 3A). OS in related BMT in the 1CR was also superior to OS in the 2CR, the 3CR, and NCR (1CR versus 2CR, $P < .0001$; 1CR versus 3CR, $P < .0001$; 1CR versus NCR, $P < .0001$; 2CR versus 3CR, $P = .0651$; 2CR versus NCR, $P = .0004$; 3CR versus NCR, $P = .8551$) (Figure 3B). In unrelated BMT, the best OS was observed in the 1CR, followed by the 2CR, the 3CR, and NCR (1CR versus 2CR, $P = .0004$; 1CR versus 3CR, $P < .0001$; 1CR versus NCR, $P < .0001$; 2CR versus 3CR, $P = .0253$; 2CR versus NCR, $P < .0001$; 3CR versus NCR, $P = .3277$) (Figure 3C). OS in allo-PBSCT in the 1CR was almost the same as that in the 2CR and the 3CR and was greater than in NCR (1CR versus 2CR, $P = .4825$; 1CR versus 3CR, $P = .8506$; 1CR versus NCR, $P < .0001$; 2CR versus 3CR, $P = .6967$; 2CR versus NCR, $P = .0142$; 3CR versus NCR, $P = .2126$) (Figure 3D). The 10-year OS rates in L1, L2, and L3 disease types were 33.1%, 31.2%, and 42.6%, respectively. L3 appeared to show a slightly better survival rate than the other disease types.

The 5-year OS rates after related BMT (n = 739), unrelated BMT (n = 695), and allo-PBSCT (n = 211) were 41.4%, 39.8%, and 28.2%, respectively. Thirty-two cases of allo-CBT followed up for 1 year showed a survival rate of 48.5%. Statistically significant differences existed between allo-CBT

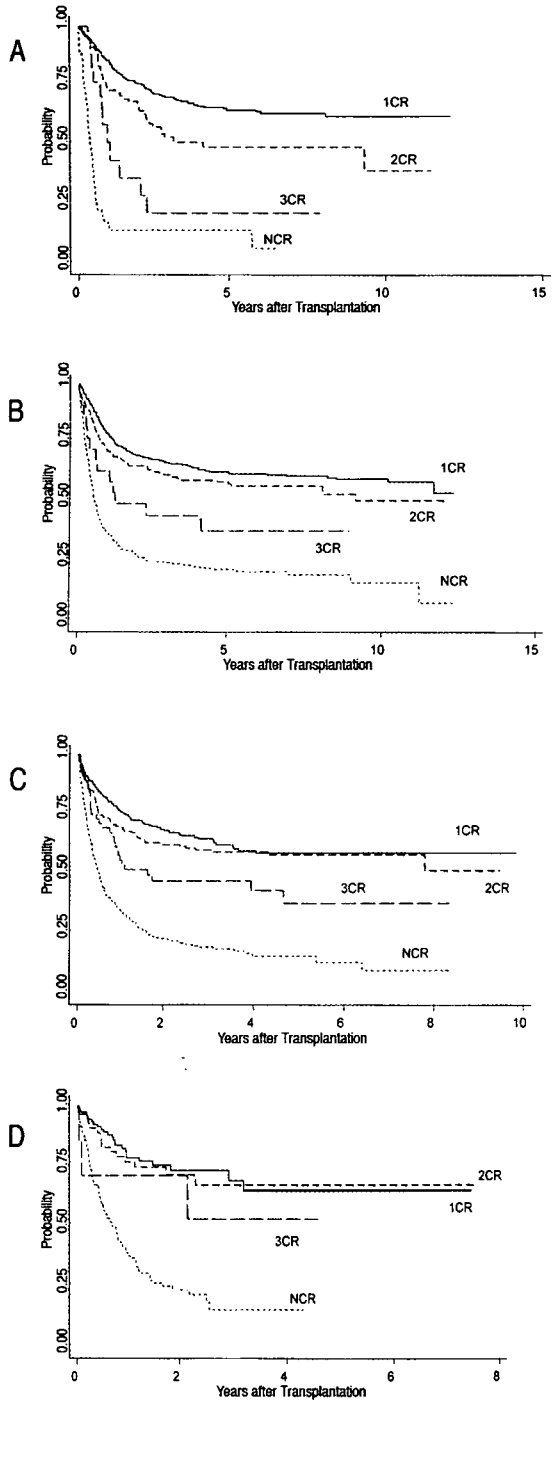


Figure 1. Overall survival (OS) in acute myelogenous leukemia. Indicated are OS in autologous hematopoietic cell transplantation (A), related allogeneic bone marrow transplantation (BMT) (B), unrelated allogeneic BMT (C), and allogeneic peripheral blood stem cell transplantation (D). 1CR indicates first complete remission; 2CR, second CR; 3CR, third CR; NCR, noncomplete remission.

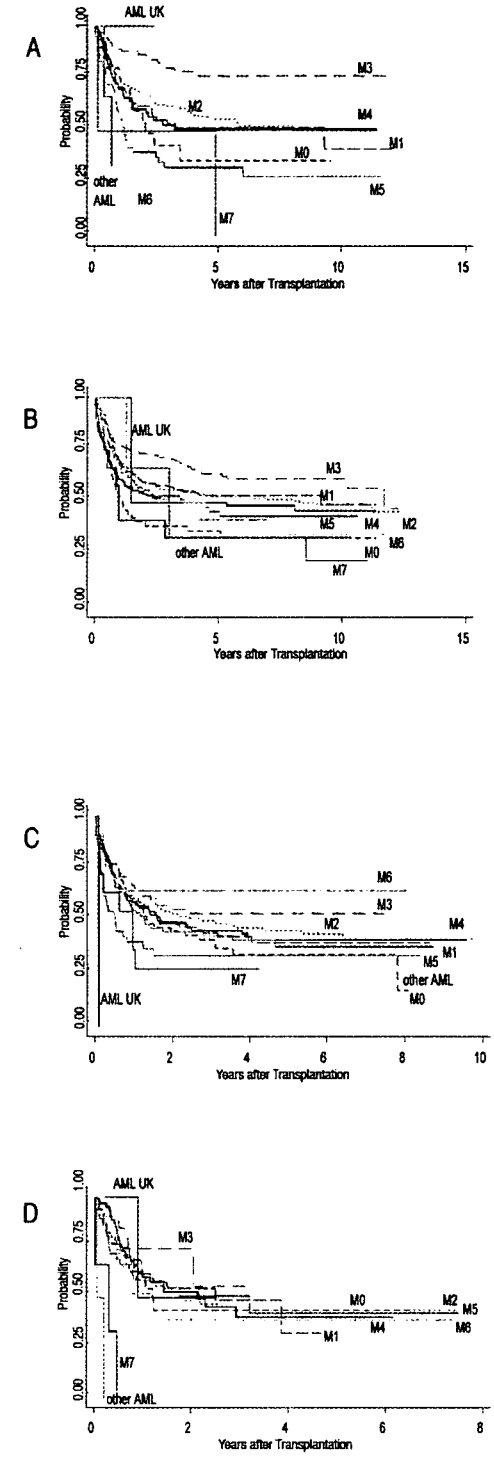


Figure 2. Overall survival (OS) in acute myelogenous leukemia (AML) by disease type. Indicated are OS in autologous hematopoietic cell transplantation (A), related allogeneic bone marrow transplantation (BMT) (B), unrelated allogeneic BMT (C), and allogeneic peripheral blood stem cell transplantation (D) by disease type according to the French-American-British classification. AML UK indicates unknown AML type, for which no definite description was reported.

Table 4.
Survival Rates in Acute Lymphocytic Leukemia Patients Who Received Autologous or Allogeneic Transplants*

	Autologous Transplantation		Allogeneic Transplantation		
Age Range, y	Time after Transplantation, y	Survival Rate, % (n)	Time after Transplantation, y	Survival Rate, % (n)	*P*
16-19	10	27.0 (55)	10	46.1 (325)	.0459
20-29	10	27.3 (68)	10	39.0 (549)	.3443
30-39	10	13.0 (33)	10	33.2 (367)	.0930
40-49	10	15.2 (47)	10	31.1 (309)	.0588
50-59	5	25.3 (39)	5	26.0 (115)	.4372
60-69	3	10.3 (10)	1	NE (6)	.7404

*Numbers of cases are indicated in parentheses. NE indicates not evaluable.

and related BMT (P = .0002) and between allo-CBT and unrelated BMT (P = .0125) when the 1-year OS rates of these groups were compared, suggesting that related and unrelated BMT were superior to allo-CBT. Furthermore, statistically significant differences existed between related BMT and allo-PBSCT (P = .0002) and between related BMT and unrelated BMT (P = .0391). A trend toward statistical significance existed between allo-PBSCT and unrelated BMT (P = .0593).

3.5. OS in Patients with CML

OS rates by age were almost the same in allo-HCT for CML, with survival rates ranging from approximately 50% to 60% except for the 42.9% OS rate in the group of patients aged 50 to 59 years (20-30 years versus 40-49 years, P = .0030; 20-30 years versus 50-59 years, P = .0037; 30-39 years versus 50-59 years, P = .0333; no statistically significant differences were apparent in any of the other age-group comparisons) (Figure 4A). In related BMT, OS in the 1CP was superior to OS in the 2CP, in the accelerated phase (AP), and in blastic crisis (BC) (1CP versus 2CP, P < .0001; 1CP versus AP, P < .0001; 1CP versus BC, P < .0001; 2CP versus AP, P = .8903; 2CP versus BC, P = .696; AP versus BC, P = .0140) (Figure 4B). Interestingly, OS in the 2CP was almost the same as that in the AP, but a worse OS was observed in BC. In unrelated BMT, OS in the 1CP was best, followed by the AP, the 2CP, and BC (1CP versus 2CP, P = .0197; 1CP versus AP, P = .0236; 1CP versus BC, P = .0181; 2CP versus AP, P = .5209; 2CP versus BC, P = .1145; AP versus BC, P = .0675) (Figure 4C), although OS in the 1CP was better in related BMT than in unrelated BMT. In contrast, it is interesting that OS in allo-PBSCT in the 1CP was almost the same as OS in the 2CP and in the AP (1CP versus 2CP, P = .2212; 1CP versus AP, P = .2729; 1CP versus BC, P < .0001; 2CP versus AP, P = .4699; 2CP versus BC, P = .0557; AP versus BC, P = .0004) (Figure 4D).

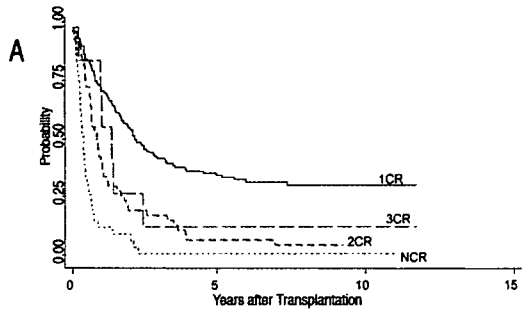
The 5-year OS rates after related BMT (n = 890), unrelated BMT (n = 858), and allo-PBSCT (n = 191) were 66.3%, 49.2%, and 59.6%, respectively. Eighteen cases of allo-CBT followed up for 1 year showed a survival rate of 61.2%. Statistically significant differences existed between allo-PBSCT and related BMT (P = .0168) and between related BMT and unrelated BMT (P < .0001), suggesting that related BMT was superior to other HCT. OS in allo-PBSCT seemed to be superior to that in unrelated BMT (P = .0684).

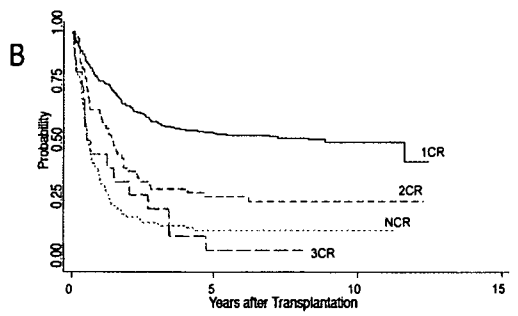
3.6. OS in Patients with MDS

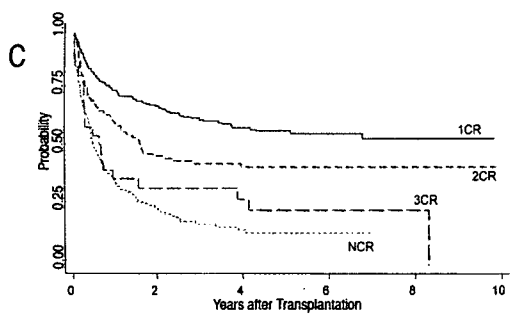
The patients aged 20 to 29 years showed survival rates that were superior to those of the other age groups, and the worst survival rate occurred in the patients aged 60 to 69 years (16-19 years versus 20-29 years, P = .0139; 16-19 years versus 30-39 years, P = .7298; 16-19 years versus 40-49 years, P = .8209; 16-19 years versus 50-59 years, P = .6306; 16-19 years versus 60-69 years, P = .0293; 20-29 years versus 30-39 years, P = .0020; 20-29 years versus 40-49 years, P = .0001; 20-29 years versus 50-59 years, P = .0001; 20-29 years versus 60-69 years, P < .0001; 30-39 years versus 40-49 years, P = .4412; 30-39 years versus 50-59 years, P = .2027; 30-39 years versus 60-69 years, P < .0001; 40-49 years versus 50-59 years, P = .4417; 40-49 years versus 60-69 years, P = .0002; 50-59 years versus 60-69 years, P = .0013) (Figure 5A).

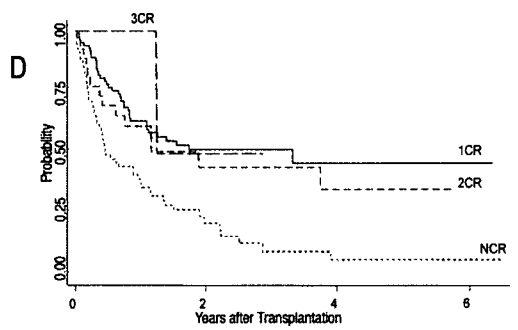
The MDS disease type was categorized according to the FAB classification (ie, refractory anemia [RA], RA with excess of blasts [RAEB], RAEB in transformation [RAEBt], RA with ringed sideroblasts [RARS], and chronic myelomonocytic leukemia [CMMoL]). In related BMT, the best OS was observed for the RA disease type (CMMoL versus RA, P = .0453; CMMoL versus RAEB, P = .7716; CMMoL versus RAEBt, P = .6404; RA versus RAEB, P = .0304; RA versus RAEBt, P = .0011; RAEB versus RAEBt, P = .2968) (Figure 5B). In unrelated BMT, the OS rates were (in decreasing order) RA, CMMoL, RAEB, and RAEBt, although statistically significant differences existed only between RA and RAEB and between RA and RAEBt (CMMoL versus RA, P = .5112; CMMoL versus RAEB, P = .5738; CMMoL versus RAEBt, P = .2854; RA versus RAEB, P = .0334; RA versus RAEBt, P = .0027; RAEB versus RAEBt, P = .4985) (Figure 5C). The same pattern was observed in allo-PBSCT (CMMoL versus RA, P = .2396; CMMoL versus RAEB, P = .7698; CMMoL versus RAEBt, P = .6954; RA versus RAEB, P = .0359; RA versus RAEBt, P = .029; RAEB versus RAEBt, P = .9199) (Figure 5D).

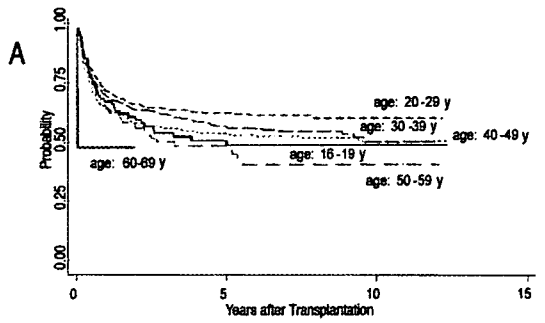
The 5-year OS rates after related BMT (n = 385), unrelated BMT (n = 323), and allo-PBSCT (n = 186) were 49.7%, 43.7%, and 33.6%, respectively. Thirty-three cases of allo-CBT followed up for 1 year showed a survival rate of 58.5%. Statistically significant differences existed between allo-PBSCT and related BMT (P = .0029) and between related

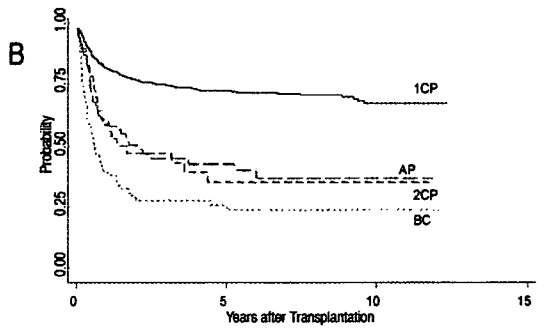


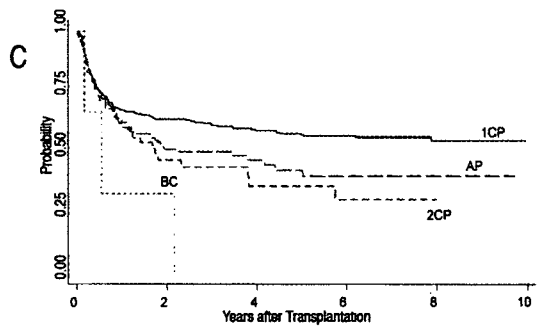












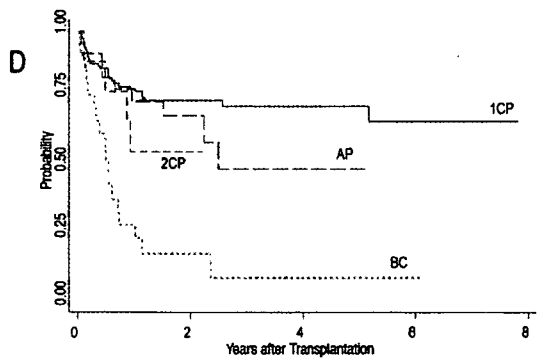


Figure 3. Overall survival (OS) in acute lymphocytic leukemia. Indicated are OS in autologous hematopoietic cell transplantation (A), related allogeneic bone marrow transplantation (BMT) (B), unrelated allogeneic BMT (C), and allogeneic peripheral blood stem cell transplantation (D). 1CR indicates first complete remission; 2CR, second CR; 3CR, third CR; NCR, noncomplete remission.

Figure 4. Overall survival (OS) in chronic myelogenous leukemia (CML). Indicated are OS in CML by age (A), in related allogeneic bone marrow transplantation (BMT) (B), in unrelated allogeneic BMT (C), and in allogeneic peripheral blood stem cell transplantation (D). 1CP indicates first chronic phase; 2CP, second chronic phase; AP, accelerated phase; BC, blastic crisis.

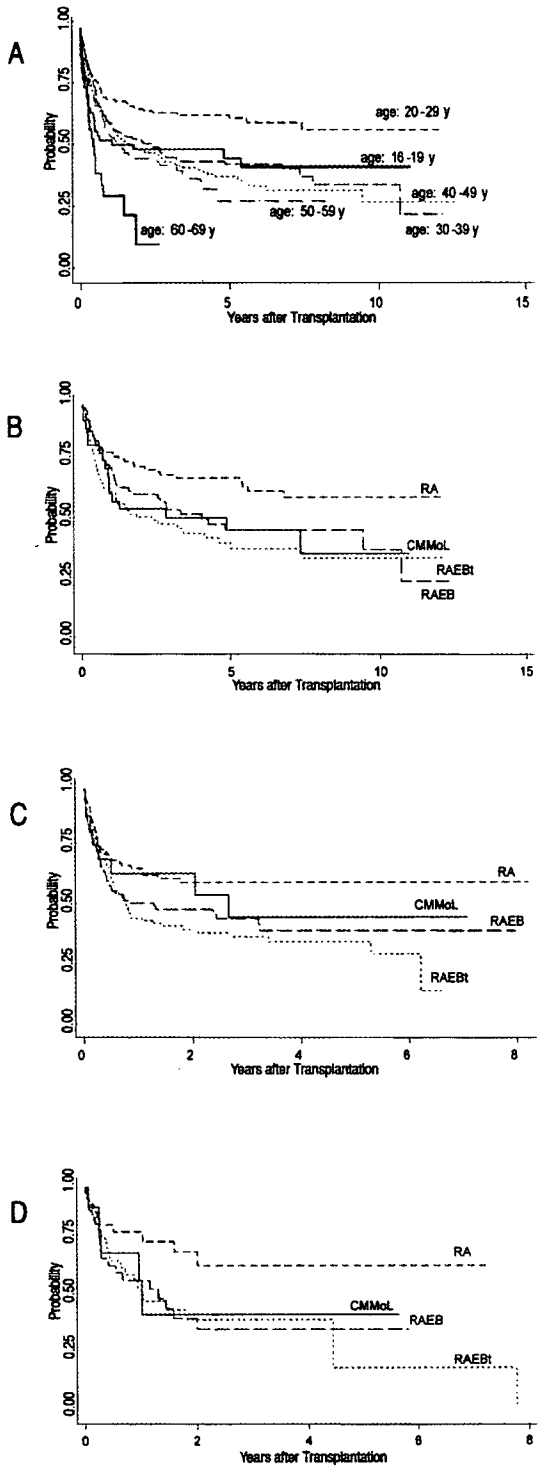


Figure 5. Overall survival (OS) in myelodysplastic syndromes (MDS). Indicated are OS in MDS by age (A), in related allogeneic bone marrow transplantation (BMT) (B), in unrelated allogeneic BMT (C), and in allogeneic peripheral blood stem cell transplantation (D) by disease type according to the French-American-British classification. RA indicates refractory anemia; RAEB, RA with excess of blasts; RAEBt, RAEB in transformation; CMMoL, chronic myelomonocytic leukemia.

BMT and unrelated BMT (P = .0018), suggesting that related BMT was superior to other HCT and that allo-PBSCT was the same as unrelated BMT in terms of the survival rate.

Ten-year OS rates after related BMT were 29.8% in MDS with leukemic transformation (n = 81) and 46.4% in MDS without leukemic transformation (n = 302) (P = .0001). One-year OS rates after unrelated BMT were 36.5% in MDS with leukemic transformation (n = 15) and 54.9% in MDS without leukemic transformation (n = 308) (P = .0369). Three-year OS rates after allo-PBSCT were 30.5% in MDS with leukemic transformation (n = 50) and 48.1% in MDS without leukemic transformation (n = 136) (P = .0584).

3.7. OS in Patients with AA

OS after allo-HCT in AA patients younger than 39 years was superior to that in patients older than 40 years (16-19 years versus 20-29 years, P = .3582; 16-19 years versus 30-39 years, P = .9859; 16-19 years versus 40-49 years, P = .0334; 16-19 years versus 50-59 years, P = .3760; 16-19 years versus 60-69 years, P = .0043; 20-29 years versus 30-39 years, P = .3501; 20-29 years versus 40-49 years, P = .0007; 20-29 years versus 50-59 years, P = .1174; 20-29 years versus 60-69 years, P = .0011; 30-39 years versus 40-49 years, P = .0312; 30-39 years versus 50-59 years, P = .3457; 30-39 years versus 60-69 years, P = .0045; 40-49 years versus 50-59 years, P = .7145; 40-49 years versus 60-69 years, P = .0650; 50-59 years versus 60-69 years, P = .1556) (Figure 6A).

OS in related BMT are shown by age group in Figure 6B (16-19 years versus 20-29 years, P = .5892; 16-19 years versus 30-39 years, P = .8268; 16-19 years versus 40-49 years, P = .0859; 16-19 years versus 50-59 years, P = .7437; 20-29 years versus 30-39 years, P = .3483; 20-29 years versus 40-49 years, P = .0058; 20-29 years versus 50-59 years, P = .4018; 30-39 years versus 40-49 years, P = .0914; 30-39 years versus 50-59 years, P = .7848; 40-49 years versus 50-59 years, P = .4770), indicating that no statistically significant differences exist between age groups.

OS of AA patients in unrelated BMT was worse than in related BMT (16-19 years versus 20-29 years, P = .7219; 16-19 years versus 30-39 years, P = .7010; 16-19 years versus 40-49 years, P = .1294; 16-19 years versus 50-59 years, P = .5207; 16-19 years versus 60-69 years, P = .4927; 20-29 years versus 30-39 years, P = .0658; 20-29 years versus 40-49 years, P = .5361; 20-29 years versus 50-59 years, P = .3099; 30-39 years versus 40-49 years, P = .4459; 30-39 years versus 50-59 years, P = .3929) (Figure 6C). Because there was only 1 patient in the group of patients aged 50 to 59 years, estimating this survival rate was difficult.

Although OS of AA patients in allo-PBSCT seemed to be better than in related BMT, the cases were too few to draw a definite conclusion (Figure 6D).

The 5-year OS rates after related BMT (n = 264), unrelated BMT (n = 129), and allo-PBSCT (n = 22) were 82.7%, 53.2%, and 69.7%, respectively. Two cases of allo-CBT followed up for 1 year showed a survival rate of 50.0%. A statistically significant difference existed between related BMT and unrelated BMT (P < .0001). Related BMT seemed to be superior to allo-PBSCT (P = .0725) in terms of the survival rate.

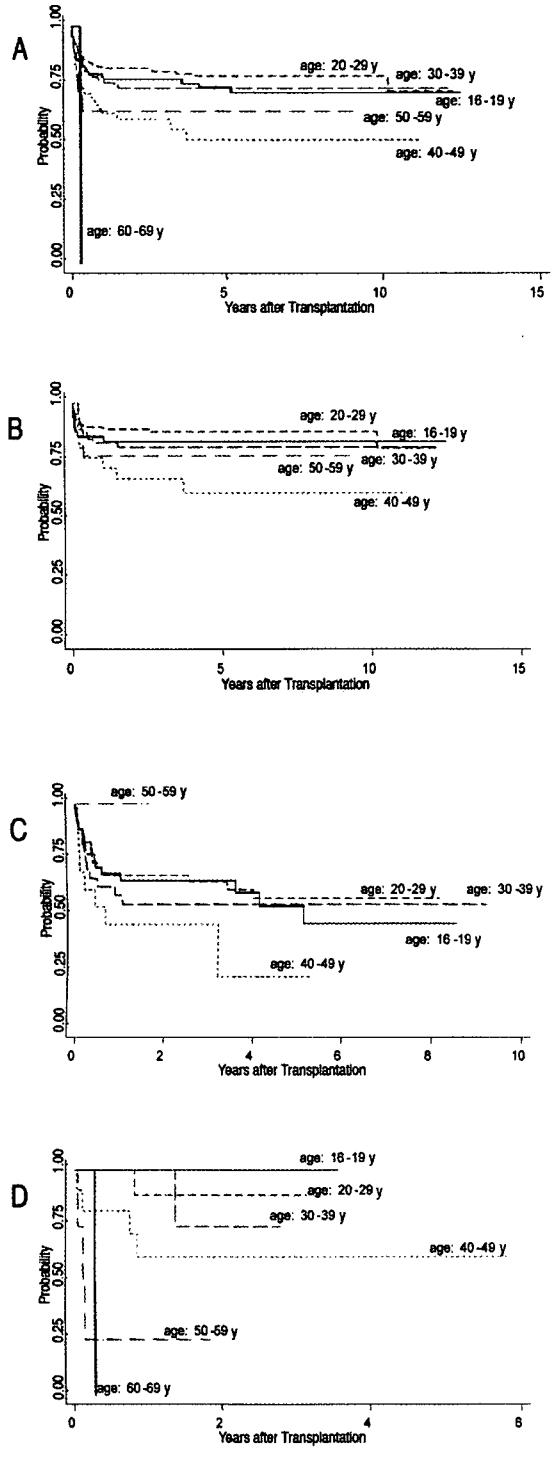


Figure 6. Overall survival (OS) in aplastic anemia. Indicated are OS by age in allogeneic hematopoietic cell transplantation (A), related allogeneic bone marrow transplantation (BMT) (B), unrelated allogeneic BMT (C), and allogeneic peripheral blood stem cell transplantation (D).

3.8. OS in Patients with NHL

OS of NHL patients in auto-HCT was worse in the patients aged 50 years or older than in those younger than 50 years (Table 5). The same trend was observed in allo-HCT (Table 5). Although OS in allo-HCT for patients aged 16 to 19 years and patients aged 60 to 69 years seemed to be superior to that in auto-HCT, the differences were not statistically significant. OS in auto-HCT was superior to that in allo-HCT in the patients aged 20 to 29 years and in the patients aged 30 to 39 years, whereas the opposite result was observed in the groups of patients aged 40 to 49 years and 50 to 59 years.

The 10-year OS rates after auto-HCT were 60.8% in the 1CR (n = 890), 39.8% in the 2CR (n = 414), 25.0% in the 3CR (n = 63), and 25.3% in NCR (n = 1090). There was a statistically significant difference ($P < .019$) among all the groups, although OS in the 3CR was almost the same as that in NCR ($P = .5253$). The 10-year OS rates after related BMT were 45.8% in the 1CR (n = 75), 57.1% in the 2CR (n = 35), 75.0% in the 3CR (n = 10), and 38.2% in NCR (n = 110). Statistically significant differences existed between 1CR and NCR ($P = .0022$) and between 3CR and NCR ($P = .0196$). The 5-year OS rates after unrelated BMT were 70.7% in the 1CR (n = 31), 61.9% in the 2CR (n = 17), 40.0% in the 3CR (n = 5), and 28.2% in NCR (n = 64). Statistically significant differences existed between the 1CR and the 3CR ($P = .0122$), between the 1CR and NCR ($P < .0001$), and between the 2CR and NCR ($P = .0015$). The difference in 5-year OS rates after allo-PBSCT (79.8% in the 1CR [n = 32] and 26.4% in NCR [n = 138]) was statistically significant ($P = .0002$).

The 10-year OS rates after auto-HCT in diffuse large cell lymphoma (DLCL), follicular lymphoma (FL), and lymphoblastic lymphoma (LBL) were 34.2% (n = 1147), 60.1% (n = 309), and 47.9% (n = 105), respectively. Statistically significant differences existed between LBL and FL ($P < .0001$) and between DLCL and FL ($P < .0001$). The 10-year OS rates after related BMT were 39.4% in DLCL (n = 47), 73.8% in FL (n = 35), and 44.0% in LBL (n = 52). A statistically significant difference existed between DLCL and FL ($P = .0020$). The respective 3-year OS rates after unrelated BMT and allo-PBSCT were 56.1% (n = 18) and 30.6% (n = 39) in DLCL, 59.5% (n = 12) and 56.7% (n = 43) in FL, and 50.1% (n = 49) and 63.0% (n = 24) in LBL. There were no statistically significant differences between the groups.

The 5-year OS rates after allo-PBSCT (n = 208), related BMT (n = 236), and unrelated BMT (n = 148) were 37.3%, 49.4%, and 45.8%, respectively. Eleven patients who received allo-CBT and underwent follow-up for only 1 year showed a survival rate of 29.1%. There was a statistically significant difference between allo-CBT and related BMT ($P = .0288$) and between allo-CBT and unrelated BMT ($P = .0363$). No statistically significant differences were observed between other groups.

3.9. OS in Patients with HL

The 10-year OS rates of HL patients after auto-HCT were 53.6% in the group of patients aged 16 to 19 years (n = 20), 56.4% in the patients aged 20 to 29 years (n = 113), 42.5% in the patients aged 30 to 39 years (n = 56), 70.2% in the

Table 5.
Survival Rates in Non-Hodgkin's Lymphoma Patients Who Received Autologous or Allogeneic Transplants*

	Autologous Transplantation		Allogeneic Transplantation		
Age Range, y	Time after Transplantation, y	Survival Rate, % (n)	Time after Transplantation, y	Survival Rate, % (n)	*P*
16-19	10	43.2 (68)	10	61.4 (66)	.2173
20-29	10	55.4 (276)	10	49.1 (128)	.0173
30-39	10	52.7 (360)	10	41.8 (129)	.0004
40-49	10	43.4 (662)	5	46.0 (154)	.0013
50-59	10	26.7 (825)	5	29.6 (110)	<.0001
60-69	5	38.5 (394)	1	60.6 (15)	.4454

*Numbers of cases are indicated in parentheses.

patients aged 40 to 49 years (n = 42), 33.7% in the patients aged 50 to 59 years (n = 20), and 25.6% in the patients aged 60 to 69 years (n = 13). The 5-year OS rates after auto-HCT were 33.7% in the group of patients aged 50 to 59 years (n = 20) and 25.6% in the patients aged 60 to 69 years (n = 13). Statistically significant differences ($P < .0293$) existed between the groups of patients aged 10 to 19 years, 20 to 29 years, 30 to 39 years, and 40 to 49 years and the group of patients aged 60 to 69 years. These results show that the OS rate in the patients aged 50 years and older was inferior to that of the patients younger than 50 years. The OS rate in the 1CR (86.5%, n = 29) was better than the OS rates in the 2CR (55.5%, n = 63; $P = .0185$), the 3CR (55.5%, n = 20; $P = .0190$), and NCR (40.0%, n = 141; $P = .0005$), thus indicating that HCT, mainly auto-HCT, must be performed in the 1CR. The 5-year OS rate after auto-HCT (64.7%, n = 265) did not significantly differ from that after related BMT (41.7%, n = 9; $P = .1208$).

3.10. OS in Patients with MM

The 5-year OS rates after auto-HCT were 80.0% in the group of patients aged 20 to 29 years (n = 5), 52.5% in the patients aged 30 to 39 years (n = 29), 45.7% in the patients aged 40 to 49 years (n = 132), 39.7% in the patients aged 50 to 59 years (n = 223), and 38.6% in the patients aged 60 to 69 years (n = 136). No statistically significant differences existed between the age groups, although OS in the younger patients seemed to be better than in the older patients. The OS rates in related BMT were 100% at 1 year in the group of patients aged 20 to 29 years (n = 1), 38.9% at 3 years in the patients aged 30 to 39 years (n = 9), 27.7% at 5 years in the patients aged 40 to 49 years (n = 31), 26.8% at 3 years in the patients aged 50 to 59 years (n = 9), and 100% at 1 year in the patients aged 60 to 69 years (n = 2). No statistically significant differences existed between the age groups. Furthermore, OS in allo-PBSCT was 62.5% at 5 years in the group of patients aged 40 to 49 years (n = 9), 38.1% at 1 year in the patients aged 50 to 59 years (n = 19), and 100% at 1 year in the patients aged 60 to 69 years (n = 3). Although OS in auto-HCT was better than in related BMT ($P = .0008$) and although OS in allo-PBSCT was better than in auto-HCT ($P < .0014$), the patients in allo-HCT, including unrelated BMT, were too few, and the observation period in allo-PBSCT and unrelated BMT was still too short.

The 5-year OS rates after auto-HCT were 44.6% in CR (n = 187), 47.0% in partial remission (PR) (n = 71), 58.2% in no change (NC) (n = 46), and 38.9% in progressive disease (PD) (n = 218). Statistically significant differences existed between the CR and PD groups ($P = .0021$), between the NC and PD groups ($P = .0399$), and between the PR and PD groups ($P = .0057$). The 5-year OS rates after related BMT were 33.4% in CR (n = 17), 30.0% in PR (n = 10), and 16.9% in PD (n = 22). There were no statistically significant differences between the groups. OS in related BMT appears to be inferior to OS in auto-HCT. Because there were still too few MM cases with related BMT and because the observation period was too short, further study is required to draw a definite conclusion.

4. Discussion

4.1. Engraftment Failure and GVHD Occurrence

A frequent problem in allo-CBT is engraftment failure [9], especially in nonmyeloablative CBT for adult patients [10]. Although this problem is most evident in nonmyeloablative HCT with CBSC, many cases of such HCT have not yet been included. Therefore, this problem may simply be a reflection of the immaturity of immunocompetent cells in CBSC, which cannot suppress the host-versus-graft reaction [11]. Nevertheless, the incidence of graft failure was very high in the present study; therefore, whether an insufficient dose of conditioning regimens and/or an insufficient amount of stem cells were used in these cases should be analyzed in future studies.

The frequencies of acute and chronic GVHD in related BMT, unrelated BMT, allo-PBSCT, and allo-CBT in Japan are generally low compared with those in Western countries, suggesting a role of genetic homogeneity and some differences in genetic background in Japan [12,13]. This speculation is also supported by the fact that clinical outcomes in unrelated HCT are worse than in related HCT in Western countries [14]. It is also supported by our observations that clinical outcomes are worse with HLA class I–mismatched donors than with HLA class II–mismatched donors, whereas the situation is completely different in Western countries [15].

4.2. OS in AML and ALL

Auto-HCT is notably more effective than allo-HCT against AML, especially for patients younger than 60 years

and in the 1CR or for patients with the M3 subtype. On the other hand, OS in auto-HCT was worse than in allo-HCT when transplantation was performed in the 2CR or the 3CR. Three large phase III studies by the European Organization for Research and Treatment of Cancer/Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto, the Medical Research Council, and the Eastern Cooperative Oncology Group (ECOG) on disease-free survival (DFS) after auto-HCT for AML in the 1CR [16-18] found that DFS was better in the auto-BMT group than in the chemotherapy group (48% versus 30%, $P = .05$), but there was no significant difference between the auto-BMT group and the allo-BMT group (DFS, 55%) [18]. Two of the 3 studies showed an overall improvement in DFS in the auto-BMT group, but none of the studies showed an improvement in OS. The improvements in DFS were particularly noteworthy in the favorable-risk cytogenetic group. In poor-risk patients, the results of the ECOG study supported allo-BMT as the treatment of choice. Although our results somewhat differed from those of these 3 studies, especially in the type of clinical study (ie, the prospective randomized study versus the retrospective study), it is not unreasonable to conclude that auto-HCT in the 1CR can be applicable to good-risk patients and that allo-HCT can be applicable to poor-risk patients, suggesting that allo-HCT is not always preferable for patients with AML. One report from Japan also supports this conclusion [19]. The role of auto-HCT for intermediate-risk patients is uncertain.

As far as disease status is concerned, allo-PBSCT is the most preferred treatment among allo-HCT for AML, regardless of disease status (except for NCR), because a better OS was observed. However, according to the disease type, allo-PBSCT did not always show a better OS than other allo-HCT treatments. It is not clear what has induced such a discrepancy. In cases of the M3 subtype, HCT is not performed in the 1CR. Therefore, auto-HCT should be preferred for M3 in the 2CR or the 3CR. For M1, M2, and M4, OS in auto-HCT in the 1CR may be comparable to OS in allo-HCT. Allo-PBSCT may preferably be performed in the 2CR and the 3CR. OS in related and unrelated BMT are almost the same, a finding that is dissimilar to that in Western countries [14].

OS in ALL was found to decrease with increasing age and could be classified into 3 groups: good (16-29 years), intermediate (30-49 years), and poor (50-69 years). OS in related and unrelated BMT were almost the same; these results are similar to the data from Western countries [20]. Auto-HCT is not applicable to ALL, which is dissimilar to AML in this respect. Related or unrelated BMT should be performed in the 1CR but not in the 2CR or the 3CR, because the status of PD correlates well with poor OS. A similar result was described in another report [21]. This situation is also completely different from that in AML. Interestingly, allo-PBSCT showed almost the same OS in the 1CR, the 2CR, and the 3CR as the OS in AML. This result indicates that allo-PBSCT may induce an antileukemic effect in acute leukemia via the allogeneic immune effect [22], although auto-PBSCT showed a beneficial effect on AML but not on ALL. AML can be readily controlled by high-dose chemotherapy (with or without irradiation) and an allogeneic immune effect, whereas ALL is generally resistant to chemotherapy and often features late relapse. However, ALL is sensitive to the allogeneic immune effect only to a limited extent. Therefore, treatment with auto-HCT is less effective for ALL than for AML. Statistics from the European Group for Blood and Marrow Transplantation (EBMT) that reveal leukemia-free survival and OS rates of 36% and 42%, respectively, in 1366 adults who underwent autografting in the 1CR [23] show a similarity to the present results. Because ALL is more resistant than AML to conventional chemotherapy and has a higher rate of failure, including late and even very late relapses, after auto-HCT and allo-HCT, the pretransplantation regimen, in vitro purging with drugs such as cyclophosphamide derivatives, and in vivo purging with imatinib mesylate for Philadelphia chromosome–positive patients should be investigated.

4.3. OS in CML

The use of allo-HCT for the up-front treatment of CML has declined in the past several years because of the development of therapy with imatinib mesylate [24]. Nevertheless, that allo-HCT with its demonstrated higher OS is the only proven curative therapy for CML has not been questioned so far. When allo-HCT, especially related BMT and PBSCT, was performed in the 1CP, the most favorable OS was obtained. It is not clear why unrelated BMT showed a worse OS than related BMT in patients in the 1CP. This result is in sharp contrast to the reports from other countries [25-27]. The reason for this discrepancy may be a lower OS in related BMT in those countries. In other words, OS in related BMT in Japan is higher than in unrelated BMT, probably because of the genetic homogeneity of the Japanese population. Even allo-HCT in the AP and the 2CP can induce a fair OS. Although it is interesting that these 2 disease statuses showed comparable OS, allo-PBSCT may be preferable for the patients in the 2CP or the AP. This situation is again similar to that in acute leukemia, suggesting that allo-PBSCT may possess more powerful antileukemia effects.

4.4. OS in MDS

Because OS in patients older than 60 years and with leukemic transformation is poor, the timing of allo-HCT should not be prolonged after diagnosis. The RA disease status has the most preferable timing. These results are comparable with those of other reports. The results indicated DFS rates of 30% to 50% and were better in patients with a younger age, low-risk scores on the international prognostic scoring system, a shorter disease duration (<1 year), no chromosomal abnormalities, and lower bone marrow blast counts. [28-30]. Unrelated BMT was almost comparable to related BMT and allo-PBSCT in OS, a result that is dissimilar to the situation in CML. On the contrary, OS in related BMT appears to be superior to that in unrelated BMT in cases of RA and overt leukemia but not in RAEB or RAEBt. These results are similar to the data from Western countries [29,31].

4.5. OS in AA

OS in AA after unrelated BMT is worse than after related BMT and allo-PBSCT. In general, OS in unrelated BMT for AA is worse than OS in related BMT. This result for AA, with survival rates ranging from 20% to 54%, is due to the high incidence of graft failure and GVHD [32-34]. Therefore, an optimal conditioning regimen, GVHD prophylaxis, and better donor selection are required to improve outcomes for patients who receive unrelated BMT [35]. The investigators in this study suggested that higher survival rates were obtained when recipients were young, transplantation was performed soon after diagnosis, an antithymocyte globulin–containing regimen was used, and donors matched at HLA-A or HLA-B were used. HLA-A, HLA-B, and HLA-DRB1 genotypic mismatches also were demonstrated in 44% of the 142 donor-recipient pairs that were matched for HLA-A, HLA-B, and HLA-DRB1 by serology. Because many HLA-A or HLA-B genotype-mismatch pairs appeared to have been included in the unrelated BMT cases that were analyzed in the present study, it is likely that OS in unrelated BMT was inferior to OS in related BMT and PBSCT for this reason. In contrast, mismatching of HLA-DRB1 was found in a National Marrow Donor Program study to be the most crucial risk factor for survival [14,36].

OS decreased in the older patients. Therefore, HCT should not be postponed when related HLA-matched donors are available. Still a matter of concern is whether related BMSC or PBSC should be chosen as the stem cell source in adults, although BMT is superior to PBSCT in children. Because OS after allo-PBSCT is poor in patients aged 50 to 59 years and 60 to 69 years, BMT is preferable for older patients. A similar tendency for a lower OS in unrelated BMT than in related BMT was seen in the present study and has been observed in the studies in other countries, suggesting that a lower survival rate is related to older age, the interval between diagnosis and transplantation, the number of transfusions, an absence of cyclosporin A for GVHD prophylaxis, a preconditioning regimen without antithymocyte globulin, and donors mismatched at an HLA class I locus [35,37].

4.6. OS in NHL and HL

There is no doubt that auto-BMT is better than salvage chemotherapy plus conventional involved-field irradiation for the treatment of chemotherapy-sensitive NHL patients who are younger than 60 years and are without any marrow or central nervous system involvement: the 5-year OS with auto-BMT is 53%, compared with 32% in the chemotherapy group [38]. Auto-HCT, especially auto-PBSCT, is mostly performed on patients with lymphoma. Although OS in NHL decreased with age, many older patients develop NHL. Thus, the timing of HCT in NHL is such that it is performed ultimately and mostly in groups of patients older than 50 years and older than 60 years, inevitably resulting in lower survival rates. OS rates in auto-HCT and allo-HCT ranged from 40% to 55% and from 30% to 61%, respectively. Superior OS were seen in auto-HCT in the patients aged 20 to 29 years and 30 to 39 years, whereas superior OS were seen in allo-HCT in the patients aged 40 to 49 years and 50 to 59 years. Whether auto-HCT should be performed in the 1CR is still a matter of controversy. Although auto-HCT is preferably performed in early-relapse patients with international prognostic index scores of 1 to 3, in patients sensitive to salvage chemotherapy, in high-risk patients sensitive to chemotherapy, or in low-risk patients resistant to chemotherapy at the time, only half of the relapsed patients survive after auto-HCT [38-40]. Therefore, to improve the outcomes in such cases, we need to develop new therapeutic strategies to overcome such limitations.

In some instances, allo-HCT can preferably be applied to patients in the 2CR and the 3CR. However, patients with NHL are usually older than 50 years; therefore, the use of myeloablative HCT is difficult for them. Nonmyeloablative HCT has recently been tried for patients with NHL, and relatively fair survival rates have been shown [41]. Furthermore, allo-HCT is superior to auto-HCT for patients with refractory or recurrent indolent NHL [42]. Therefore, nonmyeloablative HCT appears to be a promising procedure for these patients. Although such a conclusion is still premature, the use of nonmyeloablative HCT for such cases will increase in the future.

HCT for HL also mainly consists of auto-HCT, which shows a lower OS in older patients. HCT in the 1CR is better than in other disease status groups. OS in auto-HCT is close to OS in related BMT. Although the first choice would be auto-HCT because of its safety, the situation for nonmyeloablative HCT for HL may be the same as for NHL. In contrast, a graft-versus-HL effect, which has been suggested to be associated with allo-HCT in patients with relapsed or refractory HL, would reduce the probability of relapse and the incidence of secondary AML/MDS compared with auto-HCT [43]. Thus, allo-HCT should be considered as one of the curative treatments for HL. However, 2 reports from the International Bone Marrow Transplant Registry (IBMTR) and the EBMT have described disappointing results with allo-HCT in HL, suggesting that allo-HCT should play a limited role in the treatment of this disease [44,45]. The problem with these 2 studies is that most of the patients had poor-risk disease. Half of the patients in the IBMTR series had a performance status of <80% at the time of BMT, and more than 60% of the patients had evidence of active stage IV disease when they underwent BMT. The majority of patients in the EBMT series had resistant disease (primary refractory disease or resistant relapse) and B symptoms at the time of BMT. These results suggest that the poor outcomes reported by the IBMTR and the EBMT for allo-BMT in HL probably result from the selection of unfavorable-risk patients. Akpek et al [43] also found that allo-BMT produced no detectable benefit over auto-BMT in their HL patients. Thus, any advantage of allo-BMT in the treatment of HL patients with resistant disease seems to be offset by the unfavorable features of these patients.

4.7. OS in MM

Auto-HCT supported with high-dose melphalan treatment has emerged as standard therapy for MM, at least for younger patients [46-48]. No significant difference was

observed in OS by age, although there was a trend that younger patients seemed to show better OS than older patients. Regarding OS by disease status, auto-HCT should be performed in CR, PR, and NC to give a better OS. Of note is that OS in MM after auto-HCT was not affected by disease status, except for PD. The same was true for related BMT. Because the most limiting factor for allo-HCT is still the high transplantation-related mortality rate [49], especially in allo-HCT from an unrelated donor, single auto-HCT is usually performed with an unsatisfactory outcome. Therefore, ongoing trials with double auto-HCT, allo-HCT with nonmyeloablative conditioning, and auto-HCT followed by nonmyeloablative HCT are showing better OS than single auto-HCT [50-52]. Furthermore, the influence of new agents, such as thalidomide and/or dexamethasone, the thalidomide analogue lenalidomide, or bortezomib, on OS should be investigated in MM patients who receive HCT [53].

4.8. OS in Solid Tumors

Although OS in germ cell tumors and ovarian cancer after auto-HCT is fair, OS in breast cancer and lung cancer is poor. Nonmyeloablative HCT has been performed for metastatic renal cell carcinoma, and results have been promising in some cases [54,55]. However, this procedure does not always induce a sufficient effect on other solid tumors. Therefore, more sophisticated treatment strategies that clarify the mechanism of GVHD and the graft-versus-tumor effect are required to cure patients with solid tumors.

In conclusion, we have presented the current status of HCT for adult patients with hematologic and solid tumors in Japan, and the results show OS probability by stem cell source, transplant type, donor type, and transplant timing in each patient group. Because of the variability in stem cell sources, transplant types, donor types, and transplant timing, selecting an appropriate type of HCT for each patient is not easy. In fact, it is becoming more complicated. The data analyzed in this study suggest the appropriate type of HCT in some cases but not in others. However, the current analysis clearly shows what the problems are and what kinds of approaches and clinical trials should be conducted to overcome these problems.

Acknowledgments

This study is based on the nationwide survey data of the Japan Society for Hematopoietic Cell Transplantation (JSHCT). The cooperation of all participating teams and their staff, the Committee for Nationwide Survey Data Management of the JSHCT, and the Committee for Data Management in the Japan Marrow Donor Program is greatly appreciated.

References

1. Thomas ED. Bone marrow transplantation: a review. *Semin Hematol.* 1999;36(suppl 7):95-103.
2. Craddock C. Haematopoietic stem-cell transplantation: recent progress and future promise. *Lancet Oncol.* 2000;1:227-234.
3. Nieto Y, Jones RB, Shpall EL. Stem-cell transplantation for the treatment of advanced solid tumors. *Springer Semin Immunopathol.* 2004;26:31-56.
4. Gratwohl A, Baldomero H, Schmid O, Horisberger B, Bargetzi M, Urbano-Ispizua A. Change in stem cell source for hematopoietic stem cell transplantation (HSCT) in Europe: a report of the EBMT activity survey 2003. *Bone Marrow Transplant.* 2005;36:575-590.
5. Barrett J, Childs R. Non-myeloablative stem cell transplants. *Br J Haematol.* 2000;111:6-17.
6. Kanda Y, Chiba S, Hirai H, et al. Allogeneic hematopoietic stem cell transplantation from family members other than HLA-identical siblings over the last decade (1991-2000). *Blood.* 2003;102:1541-1547.
7. Izutsu K, Kanda Y, Ohno H, et al. Unrelated bone marrow transplantation from non-Hodgkin lymphoma: a study from the Japan Marrow Donor Program. *Blood.* 2004;103:1955-1960.
8. Kameoka J, Kami M, Takahashi S, et al. Clinical impact of graft-versus-host disease against leukemias not in remission at the time of allogeneic hematopoietic stem cell transplantation from related donors. The Japan Society for Hematopoietic Cell Transplantation Working Party. *Bone Marrow Transplant.* 2004;34:711-719.
9. Wagner JE, Rosenthal J, Sweetman R, et al. Successful transplantation of HLA-matched and HLA-mismatched umbilical cord blood from unrelated donors: analysis of engraftment and acute graft-versus-host disease. *Blood.* 1996;88:795-802.
10. Miyakoshi S, Yuji K, Kami M, et al. Successful engraftment after reduced-intensity umbilical cord blood transplantation for adult patients with advanced hematological diseases. *Clin Cancer Res.* 2004;10:3586-3592.
11. Madrigal JA, Cohen SB, Gluckman E, Charron DJ. Does cord blood transplantation result in lower graft-versus-host disease? It takes more than two to tango. *Hum Immunol.* 1997;56:1-5.
12. Morishima Y, Morishita Y, Tanimoto M, et al. Low incidence of acute graft-versus-host disease by the administration of methotrexate and cyclosporine in Japanese leukemia patients after bone marrow transplantation from human leukocyte antigen compatible siblings: possible role of genetic homogeneity. The Nagoya Bone Marrow Transplantation Group. *Blood.* 1989;74:2252-2256.
13. Sasazuki T, Juji T, Morishima Y, et al. Effect of matching of class I HLA alleles on clinical outcome after transplantation of hematopoietic stem cells from an unrelated donor. *N Engl J Med.* 1998;339:1177-1185.
14. Petersdorf EW, Longton GM, Anasetti C, et al. The significance of HLA-DRB1 matching on clinical outcome after HLA-A, B, DR identical unrelated donor marrow transplantation. *Blood.* 1995;86:1606-1613.
15. Morishima Y, Sasazuki T, Inoko H, et al. The clinical significance of human leukocyte antigen (HLA) allele compatibility in patients receiving a marrow transplant from serologically HLA-A, HLA-B, and HLA-DR matched unrelated donors. *Blood.* 2002;99:4200-4206.
16. Zittoun RA, Mandelli F, Willemze R, et al, for the European Organization for Research and Treatment of Cancer (EORTC) and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) Research Cooperative Groups. Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia. *N Engl J Med.* 1995;332:217-223.
17. Burnett AK, Goldstone AH, Stevens RMF, et al, for the UK Medical Research Council Adult and Children's Leukaemia Working Parties. Randomised comparison of addition of autologous bone-marrow transplantation to intensive chemotherapy for acute myeloid leukaemia in first remission: results of MRC AML 10 trial. *Lancet.* 1998;351:700-708.
18. Cassileth PA, Harrington DP, Appelbaum FR, et al. Chemotherapy compared with autologous or allogeneic bone marrow transplantation in the management of acute myeloid leukemia in first remission. *N Engl J Med.* 1998;339:1649-1666.
19. Gondo H, Harada M, Miyamoto T, et al. Autologous peripheral