The Belgian experience in unrelated donor bone marrow transplantation: identification of center experience as an important prognostic factor

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ABSTRACT

Background and Objective. We reviewed all unrelated donor bone marrow transplants (UDBMT) performed in Belgium up to December 1995 to identify prognostic factors for relapse, transplant-related mortality and survival.

Design and Methods. A total of 163 UDBMT were performed in 92 males and 71 females aged 1-55 (median 26) years. Patients were transplanted for ALL (n=35), AML (n=34), CML (n=51), other myeloid malignancies (n=14), SAA (n=21) or miscellaneous other diseases (n=8). Most patients had advanced disease; a few patients were in CR1 (n=10) or early chronic phase (CP) of CML (n=5).

Results. Overall survival at 5 yrs was 17% (95% confidence interval: 8-32%), but survival was significantly better for patients with non-malignant disorders (55% at 4 yrs). The relapse rate ±SE was projected to be 40 (28-54)% at 5 yrs, 36 (20-56)% for standard-risk and 68 (43-85)% for high-risk malignancies (*p*=0.0029). There was no relapse in CML patients transplanted in 1st CP compared to 68% at 4 yrs with more advanced CML (*p*=0.0033). Grade II-IV acute graft-versus-host disease (aGVHD) occurred in 55% by day 100 and was strongly modulated by age, ranging from 41% in <20-yr-old to 80% in >40-yr-old patients (*p*=0.0021). Transplant-related mortality (TRM) was projected to be 72 (52-87)% at 5 yrs including 2 very late deaths from lung fibrosis and secondary cancer. Main causes of death were original disease in 27, secondary malignancy in 2, GVHD in 28, interstitial pneumonia in 21, other infections in 19, and miscellaneous toxic causes in 21 patients. In multivariate analysis, the relapse rate was strongly dependent on the disease status (*p*=0.0029), TRM being significantly worse with older age (*p*=0.0049), and overall survival being significantly worse in more advanced disease (*p*=0.0006), after a second transplant (*p*=0.0166), in centers of smaller size (*p*=0.0316) and in older patients (NS).

Interpretation and Conclusions. Although results have improved somewhat in recent years, UDBMT remains a procedure with a high TRM. UDBMT should be performed in patients with less advanced diseases and in centers with more experience, particularly in the treatment of adult patients.
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Key words: bone marrow transplantation, unrelated donor, GVHD

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Allogeneic bone marrow transplantation (allo-BMT) has become the treatment of choice for a variety of hematologic malignancies, bone marrow failures and congenital disorders of the lymphohematopoietic system. However, the majority of patients who could benefit from an allo-BMT lack a suitable family donor. Therefore, registries of unrelated volunteer marrow donors have been developed in many countries, offering the possibility of unrelated donor bone marrow transplantation (UDBMT).[1-3] Compared to allo-BMT, UDBMT is usually associated with an increased risk of morbidity and transplant-related mortality (TRM)[4,5] and many physicians are therefore reluctant to propose such a transplant as early in the course of the disease as they would an allo-BMT from an HLA-identical sibling. However, similar to what has been observed for allo-BMT, outcomes are significantly worse for patients in advanced disease, both in terms of relapse and of TRM.[5,6] Therefore, it may not be the most appropriate strategy to reserve UDBMT primarily for these high-risk patients. The Marrow Donor Program (MDP)-Belgium was established to recruit volunteer donors and facilitate marrow transplants from Belgian and foreign unrelated donors. The current retrospective study was undertaken to evaluate the results of all UDBMT performed in Belgium since the first one in 1983 till December 1995. The overall results were poor and we tried to identify the reasons for this.

Design and Methods

We reviewed all unrelated donor bone marrow transplants (UDBMT) performed in Belgium up to December 31, 1995. A first questionnaire was sent to all units involved in stem cell transplantation, asking for a list of all transplants performed in their center. All centers responded and 163 UDBMT were identified. A second more detailed questionnaire was then sent for each of these cases. Essential data were obtained for all of them, although some details were missing for 10 of them. These transplants were performed by 10 teams, i.e. the Catholic University of Leuven (n=36), the University of Liège (n=30), the Catholic University of Louvain (Pediatrics) (n=22), the University of Gent (n=20), the Catholic University of Louvain (Adults) (n=19), the Free University of Brussels (n=11), University Clinics of Mont-Godinne (n=10), the Bordet Institute (Free University of Brus-

sels) (n=9), the University of Antwerp (n=3), and the Reine Fabiola Hospital (Free University of Brussels) (n=3).

There were 92 males and 71 females, aged 7 months to 55 (median 26) years. Patients were transplanted for ALL (n=35), AML (n=34), CML (n=51), other myeloproliferative disorders (n=5), MDS (n=9), NHL (n=2), multiple myeloma (n=1), SAA (n=21) or genetic diseases (n=5). Among the AML patients, 3 were in CR1, 10 in CR2 and 21 in more advanced disease. Among the ALL patients, 7 were in CR1, 17 in CR2 and 11 in more advanced disease. Among the CML patients, 27 were in chronic phase (very few (n=5) within one year of diagnosis) and 24 in accelerated phase or blast crisis. Five patients were undergoing a second transplant, 4 for leukemic relapse and 1 for graft failure.

The conditioning regimen included TBI in 125 patients, TLI in 4 and no irradiation in 27, whereas details were not available for 7 cases. The conditioning regimen consisted of an association of cyclophosphamide, Ara-C and single-dose TBI in 66 cases, cyclophosphamide and fractionated TBI in 21, TBI with miscellaneous chemotherapeutic agents in 38 or of busulfan-based regimens in 20 and other chemotherapeutic regimens in 11.

Donors were provided by the Marrow Donor Program-Belgium in 30% of the cases and by foreign registries in 70% of the cases among which the Anthony Nolan Research Center and France Transplant procured 50% of the donors. Donors and recipients were HLA-matched by serology in all but 13 cases in the direction of rejection and 9 cases in the direction of graft-versus-host disease (GvHD) (major mismatch), whereas complete data were not available for 12 cases. The mixed lymphocyte reaction was *compatible* in 100, *not compatible* in 17, not performed in 20 and non-contributive or unavailable for evaluation in 26 cases. Complete high-resolution DRB1 molecular typing was available for only 59 patients and was matched in 51 of them.

All patients received bone marrow, which was T cell depleted in 45 cases and unmanipulated in 111, with no information available for 7 cases. GvHD prevention was based on T-cell depletion in 45 patients, cyclosporine alone in 7, cyclosporine + methotrexate in 70, cyclosporine + ATG in 13, or a combination of cyclosporine + methotrexate + ATG in 17. Other agents were used in 2 patients and data were not available for 9.

Univariate actuarial survival analyses were performed using the Kaplan-Meier product-limit method and presented as % survival (95% confidence intervals). Comparisons between survival curves were made using the log-rank test. Multivariate survival analyses were carried out using the Cox proportional hazards model, with year of transplant, center (pediatric, small or large adult center), age, sex, BMT sequential number (1st or 2nd BMT), TBI (yes or no), serologic HLA match (yes or no) and type of GvHD prevention (T cell depletion, cyclosporine + methotrexate or other) as covariates. Univariate analyses were carried out with Graphpad Prism (Graphpad Software, San Diego, CA, USA) and multivariate analyses with SAS (SAS Institute, Cary, NC, USA) software.

Results

Hematopoietic recovery and GvHD

Among day 30 survivors, WBC engraftment was complete (1,000 PMN) in 94% of the cases, partial (200 PMN) in 3% and absent in 3%, while platelet engraftment was complete (100,000 Plts) in 45%, partial (20,000 Plts without transfusion) in 31% and absent in 24%. For patients surviving more than 100 days post-transplant, these figures of platelet engraftment increased to 66%, 18% and 16%, respectively.

No acute GvHD (aGvHD) was noticed in 62 patients but this includes early deaths. The maximum grade of aGvHD was grade I in 23, II in 28, III in 25 and IV in 14 patients. Data were not available in 8 patients and 3 additional patients had aGvHD that was not clearly graded. The projected rate of grade II-IV aGvHD was 55% at day 100, occurring before day 20 in half of the cases. This rate was strongly dependent on age, ranging from 41% in patients <20 yrs, to 57% in patients 20-40 yrs, and to 80% in patients >40 yrs (p =0.0021). The use of ATG did not influence the risk of aGvHD significantly. Chronic GvHD developed in 25 of 92 patients surviving more than 100 days.

Relapses

Nine patients had persisting disease despite the transplant procedure, 27 relapsed after documented CR and 28 patients not in CR at the time of transplant died too early to be evaluable for disease status.
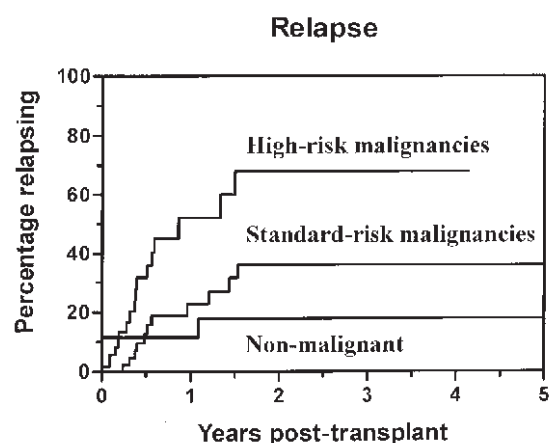

Figure 1. Kaplan-Meier estimates of the relapse rate in patients with non-malignant disorders (n=26), standard-risk malignancies (n=74) or advanced malignancies (n=63) (p=0.0029). For non-malignant diseases, "relapse" was defined as persistence or recurrence of original disease with graft rejection.

Among patients with persisting or relapsed disease after transplant, 27 died and 9 are still alive. The relapse rate was projected to be 40 (28-54)% at 5 yrs for all patients. Persistence or recurrence of original disease occurred in 18 (6-41)% for non-malignant disorders (SAA and genetic diseases), 36 (20-56)% for standard-risk malignancies and 68 (43-85)% for high-risk malignancies (p =0.0029). For AML patients, the relapse rate was 40 (18-67)% for patients in CR1 or CR2 and 63 (32-87)% for patients with more advanced disease (NS). For ALL patients, these figures were 52 (26-77)% for CR1-CR2 patients and 100% for those with more advanced disease (p =0.0015). There was no relapse in first chronic phase CML compared to 68 (32-91)% in more advanced disease (p =0.033). In the Cox analysis, only more advanced disease (p =0.0004) and GvHD prevention with cyclosporine and methotrexate (p=0.0036) were associated with a high risk of relapse.

Causes of death

At the time of this analysis, 119 patients have died and 44 are alive. The main causes of death as well as any number of contributing causes of death are presented in Table 1. Twenty-seven patients died from their original disease and 92 from transplant-related causes, including 64 patients in documented CR and 28 patients who died too early to be evaluated for disease status. Among 71 patients dying before day 100 post-transplant, aGvHD (n=18) was the leading cause of death, followed by interstitial pneumonia (n=12), other infections (n=10) and original disease (n=7). Original disease (n=20) was the leading cause of death after day 100, followed by chronic GvHD (n=9) and miscellaneous infections (n=9).
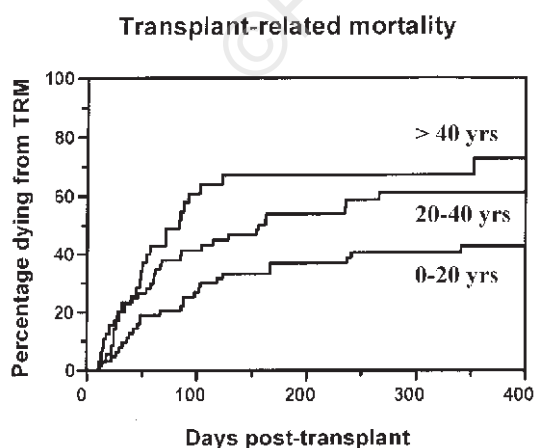

Transplant-related mortality

Figure 2. Kaplan-Meier estimates of transplant-related mortality in patients 0-20 (N=64), 20-40 (N=64) or >40 yrs (N=35) (p=0.0049).

Transplant-related mortality

Age had a major impact on survival with projected survival rates of 45%, 33% and 17% at 1 yr or 24%, 12% and 13% at 5 yrs, respectively for patients aged <20, 20-40 and >40 years (p=0.0101). This was due to a sharp increase in transplant-related mortality (TRM) from 37% to 55% to 67% for the 3 age groups, respectively (p=0.0049). Overall TRM was 50% (42-58) at 6 months and 72% (52-87) at 5 yrs because of 2 very late deaths due to idiopathic lung fibrosis and a secondary malignancy. This was not different among AML, ALL or CML patients, nor between standard-risk and high-risk malignancies. TRM tended to be lower in patients with non-malignant diseases (35% at 1 yr and 45% at 3 yrs) compared to patients with malignant disorders (60% at 1 yr and 64% at 3 yrs) (p=0.0519). In the Cox analysis, only older age was associated with a poor risk (p=0.0003).

Overall survival

Overall survival was projected to be 84% at 30 days, 56% at 100 days, 34% at one year and 17% (8-32%) at 5 through to 13 yrs (Figure 3). There was a trend for improvement in survival in the 1992-1995 period compared to earlier transplants (27% vs 14%, NS). Survival was 20% (9-39%) at 5 years in AML patients, with no difference between CR and those transplanted in more advanced disease. For ALL patients, the figure was 15% (6-33%) at 3 years with a trend for better survival in patients transplanted in CR (21% at 3 yrs) than those transplanted during more advanced disease (0% at 2 yrs) although this did not reach statistical significance. Survival for CML patients was 18% (9-33%) at

Table 1. Primary and any number of contributing causes of death in 119 patients.

|	Primary cause	Contributing cause
Original disease	27	–
Secondary malignancy	2	0
Acute GvHD	19	14
Chronic GvHD	9	6
Interstitial pneumonia	16	15
Other pneumonia	3	5
Bacterial infection	4	11
Viral infection	2	3
Fungal infection	8	20
Parasitic infection	1	0
Unclassified infection	1	4
ARDS	5	20
Graft failure	4	5
Organ failure	4	26
VOD	6	9
Hemorrhage	4	14
TTP	3	10
Unknown	1	–
Total	119	
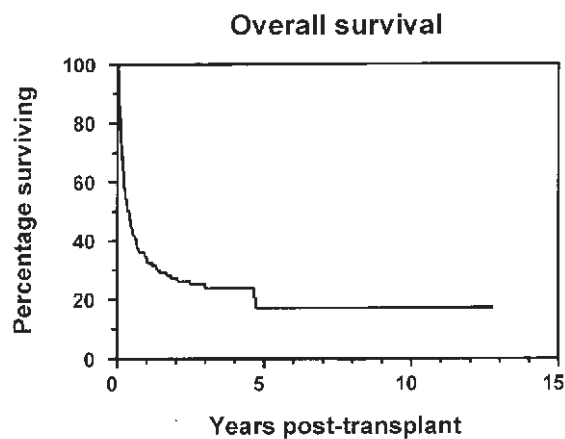
Overall survival

Figure 3. Kaplan-Meier estimates of overall survival in 163 UDBMT.

5 yrs, with better survival for patients transplanted in chronic phase than in accelerated or blast phase (32% vs 5%, *p*<0.10). Patients with standard-risk malignancies had a survival of 24% at 5 yrs, compared with 11% at 4 yrs for advanced malignancies, while those with non-malignant diseases had the best survival [55% (32-75%) at 4 yrs, which dropped to 36% (17-62%)] at 5 yrs because of the 2 very late deaths mentioned above (*p*=0.0004). In the subgroup of SAA patients, survival was 53% (30-75%) at 4 yrs and dropped to 32% (11-59%) at 5 yrs for the same reason. When comparing 45 transplants performed in pediatric centers with 66 transplants performed in larger and 52 in smaller adult centers, there was a significant difference, with 3-yr survival rates of 38%, 25% and 11%, respectively (*p*=0.0054). In the Cox analysis, more advanced disease (*p*=0.0006), second transplant (*p*=0.0166) and smaller adult center size (*p*=0.0316) were associated with poorer outcome.

Discussion

We reviewed the outcome of all 163 UDBMT carried out in Belgium up to December 1995. Overall, the results were poor, with only 17% of the patients projected to remain alive in complete remission beyond 5 years. This compares unfavorably with results published by other registries.[5-7] However, most studies report survival at 2-3 years, a significantly shorter follow-up than in our study. This is of importance, since lethal complications may occur late in this setting as illustrated by our cases of secondary cancer and idiopathic lung fibrosis. Additionally, our study encompasses many years and results have improved in the years since 1992, as observed by others.[8]

Our disappointing findings may primarily stem from the fact that most patients were in an advanced phase of their disease. One exception was transplantation for non-malignant disorders, for which we obtained good results that compare favorably with those reported in other studies,[6,9,10] probably because advanced stage is less of a problem in this setting. Of all possible factors influencing the outcome of UDBMT, disease status at transplant is of major importance.[3,5] The relationship between disease status and outcome of UDBMT has been particularly well established for CML, acute leukemias and MDS.[5,7,11-14] Patients with more advanced disease not only relapse more frequently, but also have a higher risk of TRM,[5,12] probably because of extensive previous treatments. Even within the group of patients with CML in first CP, survival is significantly worse for patients transplanted beyond one year after diagnosis.[12] In our series of patients, very few were transplanted within one year of diagnosis of CML, which might explain why survival was only 32% in CML patients transplanted in CP. Similarly, the relapse rate in ALL CR2 was high even compared with those reported for poor-risk patients,[15] and this may reflect the use of single dose instead of fractionated TBI in some patients.

The reasons for transplanting patients late in the course of their disease include the time necessary to find a donor and the reluctance of physicians to propose a procedure perceived as highly risky until no other option is available. The time from search initiation to transplant has been reduced in recent years by increasing the donor pool and emphasizing prospective complete HLA-typing, including molecular typing, of donors newly recruited into registries.[7,8] Recent studies have shown that in some instances outcomes of UDBMT were comparable to those of allo-BMT from a matched sibling[16,17] or those of autologous BMT.[18] Results obtained by some individual teams in CML patients transplanted in early chronic phase are extremely encouraging,[12,19] particularly when no interferon-α has been given.[20] These results should now convince physicians to consider UDBMT as a valid first-line option for younger CML patients or selected patients with poor-risk acute leukemia.

Among patient characteristics influencing survival after UDBMT, age, consecutive number of transplant and HLA-matching are usually considered as the most meaningful. Marrow cell dose also is now recognized as an important factor.[14] Second transplants for relapse or graft failure after autologous BMT or UDBMT are associated with an increased risk of TRM as well as disease resistance.[6] Results in children are uniformly better than in adults, partly due to an increased incidence of severe acute GvHD and extensive chronic GvHD with older recipient age.[7,8,10,11,13,16,21-25] Although HLA matching did not emerge as a significant prognostic factor in our analysis, it is now considered of critical importance for the outcome of UDBMT. This was evident for HLA matching by serology in adults,[5-8,26] possibly resulting in

a low incidence of GvHD in some patient populations closely matched to their donors.[27,28] This was much less evident in children in whom one minor (split antigen or DRB1 molecular) mismatch or major (broad antigen) mismatch was not associated with poorer outcome.[21-25] The recent availability of molecular typing may improve the degree of matching, thus reducing the risk of severe GvHD and improve outcome.[29] The risk of severe GvHD and TRM can be reduced by matching for HLA-C,[30,31] HLA-DRB1,[32] HLA-DQB1,[33] as well as HLA class I alleles,[34] but not for HLA-DPB1.[35] High resolution HLA matching combining several techniques can thus result in decreased mortality after UDBMT.[3,36] This may explain the better results obtained by us and other groups in more recent years.

Pediatric centers treated younger patients of whom a higher proportion had non-malignant disorders; their results were superior to those obtained in adult transplant centers. Individual center's experience of UDBMT was also very important. Among adult transplant centers, outcome was superior in centers with greater experience compared with smaller centers. This was true even if the only adult center transplanting younger patients with less advanced diseases (and obtaining better results than the others) was one of the small centers. This confirms the findings of the IMUST study[4] and emphasizes the need for a considerable experience when carrying out these high-risk procedures.

Contributions and Acknowledgments

M-FD conducted the study, analyzed the data and wrote the paper. MBo, CV, LN, AFerr, RS, CD, DB, ZB, AFers, YBen, HD and YBeg took care of the patients and reviewed the manuscript. The order of their names reflect the number of patients under their care. YBeg designed the study, analyzed the data and wrote the paper.

Disclosures

Conflict of interest: none.
Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

Manuscript received January 12, 1999; accepted May 10, 1999.

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