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Immunogenetic, clinical and organizational factors in unrelated hematopoietic stem cell donors searches for patients with hematological diseases

Introduction

Hematopoietic stem cell transplantation (HSCT) is a recognized, effective and widely used method of malignant and non-malignant hematopoietic diseases or immune disorders. The largest group are allogeneic transplants (allo-HSCT) from an unrelated donor. Many disease related (i.e. type and stage of the disease) or recipient related (i.e. age, comorbidities) factors influence the results of hematopoietic stem cell transplantation from an unrelated donor. The availability of a suitable donor is the basic condition for the success of allo-HSCT, and its immunological and biological characteristics determine the success of the procedure. Not only the immunogenetic tissue compatibility of the donor-recipient pair but also the source of stem cells, donor age and sex, the anti-infectious immunity status of the donor and the recipient against viruses (CMV, EBV) and other pathogens, blood group compatibility and other determinants may influence the transplant result. The outcome after HSCT and transplantation-related mortality may also be influenced by organizational factors, such as the time to transplantation, conditioned by the availability of donors in registries and efficient organization of donor search and selection.

Aims of this study

1. To define immunogenetic, biological, clinical and organizational determinants of unrelated donor selection procedures.

2. To analyze the unrelated donor selection procedures for patients with haematological diseases carried out in 2001-2015 at the request of the Polish Transplant Coordinating Centre Poltransplant.
3. To analyze the clinical data and results of transplantation procedures in the group of the above-mentioned recipients.
4. To evaluate the impact of individual selection determinants on the transplantations results and to establish their hierarchy.
5. To show that organizational factors are an important element of the donor selection procedure.
6. To assess the possibility of the most optimal donor-recipient pair selecting and to attempt developing an extended unrelated donor selection algorithm, taking into account the results of above analysis of donors searches and selection procedures as well as own experiences.

Material and methods

The study analyzed the unrelated donors selection procedures carried out between 2001 and 2015 by selected Search Centers at the request of the Polish Transplant Coordinating Centre Poltransplant and their impact on the transplantation result. In the research process, data on 1,131 recipients were collected - 29.44% pediatric patients (n = 333) and 70.56% (n = 798) patients over 18 years old. The average age of the recipients was 29 years (range 0.18 - 66 years, median = 28). The average age of adult recipients was 38 years (range 18 - 66 years, median = 38) and 9 years (0.18 - 18 years, median = 8) for pediatric patients. There were 653 men and 477 women among the patients, 57.74% and 42.17% of the study group, respectively. The observation period of the study group ranged from 18 days to 11 years from the moment of transplantation. The end point of follow-up was the date of last contact or

the date of death. At the time of qualification for the unrelated donor search and selection procedure, the patients suffered from malignant diseases (n = 995), non-malignant hematopathies (n = 83) or metabolic diseases and immune disorders (n = 53).

The basic criterion for the selection of the donor-recipient pair was the compatibility of HLA antigens - A, B, C, DRB1, DQB1 at the high resolution level. Extended MHC haplotype (Ehp) disparity was also assessed. Depending on the availability of donors in the registries, biological selection factors were also taken into account: donor age, sex, blood group, CMV status, number of pregnancies and transfusions.

The endpoints of this retrospective analysis were long-term overall survival (OS) from the date of HSCT to all-cause death and relapse free survival (RFS) from HSCT to relapse or all-cause death. For selected factors, transplant-related mortality (TRM) and relapse incidence (RI) were also assessed.

Results

For 1,127 (99.64%) recipients, the procedure was completed with donor selection, in 1,126 cases an unrelated donor and in one case a haploidentical donor. Unrelated donors came from the national registry n=402 (35.70%) and from foreign registries n=724 (64.30%), most often from the German registry – 583 (51,55%) donors.

Finally 1,092 (91.12%) patients were transplanted, including 761 recipients over 18 years old and 331 pediatric recipients - 69.69% and 30.31% of the study group, respectively. For n=759 (69,51%) recipients the hematopoietic stem cells came from a fully matched donor, n=273 (25%) times from a 9/10 donor and in 60 (5,49%) cases from donors with two HLA mismatches (8/10). Peripheral blood (PBSC) was the source of hematopoietic stem cells in n=819 (75%) cases, for n=252 (23.08%) recipients it

was bone marrow (BM), and in the remaining 21 (1.92%) cases transplantation centers did not report cell source.

Longer survival was observed in the group of pediatric patients and in the group of female recipients (63% vs 53%, p=0,0044). The best results of transplantation were observed in patients with non-malignant diseases (p=0,00006) and in recipients after transplantation in the first complete remission (OS: 62% vs 51%, *p*=0,0012). The impact of HLA and Ehp compatibility on the overall survival and transplant-related mortality were also demonstrated. In the total group of 1,092 recipients, the highest probability of survival was observed after transplantation from a fully matched donor, the lowest from a donor with two HLA mismatches (donor 8/10) (58% vs. 47%, p=0.0395). In the group of adult recipients, an HLA compatibility impact of the relapse free survival (RFS) was also observed (79%, 73%, 77%, p=0.0488). Also compatibility of extended MHC haplotypes (Ehp) correlated with better overall survival (OS) in the observed group of patients (60%, 54%, 44%, p=0.0920). The impact of donor age and sex, blood group and CMV status compatibility on transplantation results was also observed. The importance of organizational factors as well as the availability of donors in Polish and foreign registries were also extensively analyzed, and a significant impact of this factors on overall survival after transplantation was observed.

Conclusions

1. Donor selection is an important element of the transplant procedure.
2. The applied donor selection criteria affect the transplantation results measured by overall survival, relapse free survival, transplant-related mortality and relapse incidence.

3. The most important unrelated donor selection factors are: compatibility of HLA, extended MHC haplotype (Ehp) in the case of donors with HLA mismatch, donor age and duration of the selection procedure.
4. Organizational factors significantly affect the result of transplantation from an unrelated donor.
5. Shortening the selection time and the time to transplantation is of crucial importance for the outcome after HSCT.
6. Financing the selection procedures and the Algorithm for finding and selecting an unrelated donor proposed by the Poltransplant should take into account the benefits for the patient resulting from shortening the selection time.
7. The proposed algorithm for selecting an unrelated donor takes into account the analysis of individual donor specific criteria which is the subject of this work, own experience and literature data.
8. It is also important to monitor the duration of procedures in the Central Bone Marrow Donor Registry, realized by individual donor centers at the donor activation stage in unrelated donors searching and matching procedures for domestic and foreign recipients as well as in foreign registries. This should be taken into account when creating a new informatic system of the register.