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Sex-specific survival difference in association with HLA-DRB1∗04 following allogeneic haematopoietic stem cell transplantation for lymphoid malignancies

Katalin Balassa[a,*], Hajnalka Andrikovics[a,e], Peter Remenyi[b], Arpad Batai[b], Aniko Szilvasi[c], Andras Bors[a], Katalin Piroska Kiss[a], Katalin Rajczy[d], Dora Inotai[c], Eva Torbagyi[b], Lilla Lengyel[b], Aniko Barta[b], Laszlo Gopcsa[b], Attila Tordai[a,e], Tamas Masszi[b,f]

[a] Laboratory of Molecular Diagnostics, Hungarian National Blood Transfusion Service, Budapest, Hungary
[b] Department of Haematology and Stem Cell Transplantation, St. Istvan and St. Laszlo Hospital, Budapest, Hungary
[c] Transplantation Immunogenetics Laboratory, Hungarian National Blood Transfusion Service, Budapest, Hungary
[d] Hungarian Stem Cell Donor Registry, Hungarian National Blood Transfusion Service, Budapest, Hungary
[e] Department of Pathophysiology, Semmelweis University, Budapest, Hungary
[f] 3rd Department of Internal Medicine, Semmelweis University, Budapest, Hungary

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ABSTRACT

The role of HLA system in allogeneic haematopoietic stem cell transplantation (allo-HSCT) outcome is unarguable. In this study we investigated association of HLA-A,-B and-DRB1 alleles with overall survival (OS) in 186 patients undergoing allo-HSCT for lymphoid malignancies. Analyses confirmed significantly better OS for HLA-DRB1∗04 carriers compared with non-carriers ($p = 0.01$). Survival benefit was confined to male patients (in multivariate analyses $p = 0.034$, hazard ratio 0.35, 95% confidence interval 0.13–0.92), whereas in females no difference was noted ($p = 0.82$). Furthermore, donor gender also affected outcome and transplantation from female HLA-DRB1∗04 carrier donors resulted in superior survival compared with female non-carrier donors ($p = 0.01$). Combined analyses including recipient/donor gender and HLA-DRB1∗04 showed that survival of male patients varied significantly according to donor gender and HLA-DRB1∗04 carriership ($p = 0.04$) with best survival among HLA-DRB1∗04 carriers transplanted from female donors. Of relevance to our results, HLA-DRB1∗04 has been documented as risk allele group for lymphoid malignancies, and studies described a male-specific risk. We believe that our findings provide further supporting evidence for sex-specific alterations secondary to HLA-DRB1∗04 or related genes. Further studies are warranted to evaluate whether in contrast to general favour of male donors HLA-DRB1∗04 carrier patients with lymphoid malignancies could benefit from transplantation from female donors.

1. Introduction

The major histocompatibility complex (MHC) is the most polymorphic genetic system in the human genome [1]. The MHC region contains a large number of multiply linked genes, including two major clusters of the classical human leucocyte antigen (HLA) genes, the class I and II, encoding for HLA-A, -B, -C and HLA-DR, -DQ, -DP, respectively [2]. The diversity of HLA genes in different ethnic groups has been increasingly evaluated for the purposes of allogeneic haematopoietic stem cell transplantation (allo-HSCT), with the aim to improve the probability for unrelated donor search and to lower the risk of post-transplantation complications via optimal HLA-matching [3–5]. Based on its fundamental role in immune responses, the MHC region has been the focus of many studies investigating outcome parameters following allo-HSCT, which revealed several associations with survival, relapse and graft-versus-host disease (GvHD) [1].

Moreover, the HLA system has been extensively studied for the exploration of disease associations [2]. The first human disease with

Abbreviations: Allo-HSCT, allogeneic haematopoietic stem cell transplantation; ALL, acute lymphoid leukaemia; CI, confidence interval; CLL, chronic lymphoid leukaemia; CMV, cytomegalovirus; CR, complete remission; CSA, cyclosporine; EBV, Epstein-Barr virus; GvHD, graft-versus-host disease; HL, Hodgkin lymphoma; HLA, human leucocyte antigen; HR, hazard ratio; MAC, myeloablative conditioning; MHC, major histocompatibility complex; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma; OS, overall survival; P, probability value; RIC, reduced intensity conditioning; TAC, tacrolimus; TRM, transplantation-related mortality

∗ Corresponding author at: Laboratory of Molecular Diagnostics, Hungarian National Blood Transfusion Service, Karolina str 19-21 Budapest, 1113 Hungary.
E-mail address: katalin.balassa@nhs.net (K. Balassa).

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confirmed MHC haplotype relationship was paediatric acute lymphoid leukaemia (ALL) in 1970 [6]. To date, numerous studies have been conducted to establish associations of the HLA system with lymphoid leukaemia and lymphoma [7–9]. Interestingly, the distribution of the risk genes have showed sex-specific alterations in a number of studies, such as in ALL a male-specific increase for HLA-DRB1∗04 has been detected [8,10]. However, negative association studies have also been reported [11].

The aim of the hereby presented work is to assess the prognosis of adult patients with lymphoid malignancies undergoing allo-HSCT according to carriership of HLA-A, -B and -DRB1 allele groups, and analyse whether the HLA loci, which have been proposed as predisposing ones for lymphoid tumours could have an impact on the outcome of carriers following transplantation.

2. Materials and methods

2.1. Patient cohort

The study included 186 consecutive, Caucasian, adult patients, who underwent first allo-HSCT between January 2007 and December 2013 at our single centre in Hungary, for ALL (n = 75), non-Hodgkin's lymphoma (NHL, n = 42), chronic lymphocytic leukaemia (CLL, n = 26), multiple myeloma (MM, n = 25) or Hodgkin's lymphoma (HL, n = 18). All but in five cases peripheral blood was the graft source. The majority of ALL patients were transplanted in complete remission (CR, [66/75, 88%]), whereas only a quarter of patients suffering from other lymphoid malignancies achieved CR prior to transplant (28/111, 25%). There were 106 patients (57%) transplanted from a sibling and 80 (43%) transplanted from a matched unrelated donor. In the entire cohort five patients (3%) received a graft, mismatched for HLA-A, twenty-one (11%) for HLA-C and none for HLA-B or HLA-DRB1 at the antigen level. Mismatched transplants were not excluded from the cohort due to the low numbers, but multivariate analysis models were systematically adjusted for mismatching. The study was approved by the Hungarian National Ethics Committee and conducted in accordance with the Helsinki Declaration. All patients provided informed consent.

2.2. HLA typing

Whole genomic DNA was isolated from peripheral blood or bone marrow by standard commercial kits, following the manufacturers' instructions. HLA tissue typing was completed at the Transplantation Immunogenetics Laboratory of the Hungarian National Blood Transfusion Service. Low resolution HLA-A, -B, -C and -DRB1 typing for recipients and donors in the sibling donor setting were performed by polymerase chain reaction with sequence-specific primers (SSP, Olerup, Stockholm, Sweden) or sequence-specific oligonucleotide probes (SSOP, One Lambda, Los Angeles, CA, USA). In unrelated HSCT high resolution HLA-typing was carried out by high resolution SSP (Olerup, Stockholm, Sweden) or sequence based typing (SBT, Qiagen, ROSE, Valencia, CA, USA).

2.3. Statistical methods

HLA-A, -B and -DRB1 allele group frequencies (AF) for patients were calculated by direct counting. Of the detected 15 HLA-A, 27 HLA-B and 13 HLA-DRB1 allele groups the ones with an allelic frequency above 5% were included into the survival analyses. For analyses high resolution HLA typing results were converted to low resolution, and associations with the allele groups were tested. Statistical analyses for categorical variables were performed by the $\chi 2$ or the Fisher's exact tests and for continuous variables by Mann-Whitney test. Overall survival (OS) was defined as survival from the day of transplantation until death or last follow-up. OS data were analysed by the log-rank test and Kaplan-Meier estimates were computed. In multivariate survival analyses Cox proportional hazard models were adjusted for age, recipient and donor gender, diagnosis, remission status at transplantation (complete remission [CR] vs. no CR), donor type (sibling vs. unrelated), HLA-matching (8/8 vs. less than 8/8), conditioning intensity (myeloablative vs. reduced intensity) and immunosuppressive regimen (cyclosporine vs. tacrolimus). Cause of mortality was defined as disease-related mortality in case of death from relapse/progression or transplantation-related mortality (TRM) if death was secondary to any other cause. Cumulative incidences of acute GvHD and CMV reactivation/disease were calculated by the Fine and Gray model, with death included as a competing risk into the analyses [12]. The analyses were carried out with SPSS Statistics 22 (Armonk, NY, USA) and SAS (Statistical Analyses Software, Cary, NC, USA).

3. Results

3.1. HLA-A, -B, -DRB1 frequencies

In the patient cohort statistical analyses were completed for the following allele groups, for whom the allele group frequency exceeded 5% in the patient cohort (listed from highest to lower AF); HLA-A∗02, ∗01, ∗03, ∗24, HLA-B∗44, ∗18, ∗35, ∗08, ∗07, ∗51, ∗15, ∗40 and HLA-DRB1∗11, ∗07, ∗03, ∗13, ∗01, ∗04, ∗15, ∗16 (Table 1).

3.2. Survival of patients according to HLA-A, -B, and -DRB1 loci

186 patients with a median age of 42 years (range 19–67) at transplantation underwent allo-HSCT for lymphoid malignancies between 2007 and 2013 at our single centre. The median follow-up time for surviving patients was 44 months (range 8–100). Patient, donor and transplantation characteristics for the entire patient cohort and for patients diagnosed with ALL or other malignancy are presented in Table 2. Kaplan-Meier analyses of the cohort confirmed that the survival of those, who were transplanted in complete remission (p = 0.002) and/or from a sibling donor (p = 0.03) was significantly better. Examining the role of HLA status on survival, analyses showed that carriers and non-carriers displayed no survival difference for any of the HLA-A or -B allele groups. However, tests confirmed that patients carrying HLA-DRB1∗04 experienced significantly better overall survival compared with non-carriers (24-month OS 66 ± 8% [n = 36] vs. 50 ± 4% [n = 150], p = 0.01, Fig. 1). The distribution of the HLA-DRB1∗04 alleles was the following, DRB1∗04:01 36.8%, DRB1∗04:02 10.5%, DRB1∗04:03 13.2%, DRB1∗04:04 21.1%, DRB1∗04:05 2.6%, DRB1∗04:07 5.3%, and DRB1∗04:08 10.5%. None of the other HLA-DRB1 allele groups showed an association with survival, neither was a survival difference observed for carriers of HLA-DRB1∗04, ∗07 and/or ∗09 when combined together for analyses compared to carriers of other HLA-DRB1 allele groups. Comparison of the baseline characteristics

Table 1
HLA-A, -B, and -DRB1 allele group frequencies (%) in the entire cohort of patients with lymphoid malignancies (n = 186) and in the ALL subgroup (n = 75). (Allele groups with a frequency exceeding 5% are listed and ranked according to their frequencies in the entire cohort.)

HLA-A			HLA-B			HLA-DRB1		
	Entire cohort	ALL		Entire cohort	ALL		Entire cohort	ALL
A*02	30.4	31.3	B*44	10.5	12.0	DRB1*11	18.3	18.0
A*01	15.3	15.3	B*18	9.9	10.7	DRB1*07	12.1	10.0
A*03	11.6	11.3	B*35	9.9	8.0	DRB1*03	11.8	12.7
A*24	10.8	10.7	B*08	8.3	11.3	DRB1*13	10.7	11.3
			B*07	7.8	7.3	DRB1*01	10.2	10.7
			B*51	6.7	8.0	DRB1*04	10.2	14.0
			B*15	6.4	10.0	DRB1*15	9.1	10.7
			B*40	6.2	5.3	DRB1*16	5.6	4.0