Allogeneic haematopoietic stem cell donation and transplantation across the MHC class I barrier: "Faster is better than more. More is better than less".

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Acceptable MHC class I mismatches in haematopoietic stem cell transplantation.

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Submitted

Too many differences between a scarecrow and a human being

Abstract

A fully MHC matched donor is not available for the majority of patients in need of a haematopoietic stem cell transplantation (SCT), which illustrates the need of a tool to define acceptable MHC disparities. Previously, we noticed that a variety of single MHC class I mismatched allogeneic donor-recipient pairs did not elicit an allogeneic CTL response in vitro, if the MHC amino acid sequences had five or more differences in the α helices plus five or more differences in the β sheet (≥5α5β). To address the clinical relevance of this observation we analysed CTLp assay outcome and SCT outcome of 53 Dutch recipients of a single MHC class I mismatched graft from an unrelated donor. Overall patient survival was 44% after 4 years. In multivariate analysis, recipients of a ≥5α5β mismatched graft with negative CTLp frequencies in vitro prior to transplantation demonstrated superior survival: survival at 4 years was 80% as compared to 47% in recipients of other mismatched grafts with negative CTLp frequencies (hazard ratio = 0.131; 95% CI = (0.03-0.60); p = 0.009). This option of acceptable mismatches may enlarge the pool of potentially compatible stem cell donors.

Introduction

Allogeneic haematopoietic stem cell transplantation (SCT) remains the most effective curative option for a variety of haematological disorders such as leukaemia's and bone marrow failure syndromes. Due to the discrepancy between demand and supply of human leukocyte antigen (HLA) matched stem cell donors it is inevitable in many cases to transplant stem cells from HLA mismatched donors.[1-4] However, this results in an increased incidence of life threatening graft versus host disease (GVHD), graft failure and severe viral infections. [5,6] Recently, we showed that there is an upper limit to the degree of major histocompatibility complex (MHC) class I amino acid sequence disparity that elicits an allogeneic T cell response in vitro.[7] In a Cytotoxic T-Lymphocyte precursor (CTLp) assay, HLA-C differences with five or more amino acid differences in the α helices as well as five or more in the β sheet (≥5α5β) did not elicit an allogeneic CTL response in all but one case. This finding might be useful when selecting haematopoietic stem cell donors for transplantation as several studies have shown the CTLp assay to be a clinically relevant parameter for the assessment of SCT outcome.[8-13] An upper limit to the degree of MHC amino acid sequence disparity recognisable by T cells is in agreement with the theories on T cell selection processes within the thymus. In generating a T cell repertoire with a sufficiently narrow responsiveness for self-MHC, positive thymic selection limits the capacity to recognise MHC molecules of which the structure and sequence have diverged extensively.[14-18] Many ≥5α5β mismatched MHC class I molecules will fall into this category of extensively diverged MHC molecules. If no T cell alloreactivity against a ≥5α5β mismatch can be measured in vitro we expect that transplantation across a ≥5α5β mismatch will not lead to T cell alloreactivity after transplantation in vivo.

We therefore question whether there is a difference between the prognostic value of a negative CTLp assay performed on a single ≥5α5β MHC class I mismatched pair and a single less diverged MHC class I mismatched pair. Not all peptides presented by MHC class I in the recipient have been presented by the recipients peripheral blood lymphocytes in the CTLp assay.[19] If less diverged class I MHC on other cell types in the recipient present peptides specific for these tissues, a CTL alloimmune response could be triggered, even in case of a negative CTLp assay before transplantation. Whether this is the case for ≥5α5β mismatched MHC is open to question. If the donor T cell repertoire is unresponsive to recipient ≥5α5β mismatched MHC, than it should not matter which peptide is presented by the ≥5α5β MHC of the recipient. To investigate whether SCT with a single ≥5α5β MHC class I mismatched graft leads to successful transplant outcome we analysed the follow up records of a group of Dutch patients transplanted with a single MHC class I mismatched graft. As the ≥5α5β was not known at the time of transplantation there is no selection bias. In this report we address two questions. The first is whether we can subdivide the donor-recipient pairs with a negative CTLp assay into a prognostic favourable and unfavourable group by distinction between the pairs being respectively ≥5α5β MHC class I mismatched or not. Secondly, can the ≥5α5β MHC class I mismatch category replace the CTLp assay as a prognostic tool for SCT outcome.

Materials and Methods

Donor/recipient pairs

The studied cohort of donors and recipients that were transplanted between 1992 and January 2004 contained 74 pairs. The transplantations, registered by the Europdonor Foundation, took place in the following Dutch haematopoietic stem cell transplantation centres: Leiden University Medical Centre in Leiden (n=40), Erasmus MC/Daniel den Hoed in Rotterdam (n=23), and University Medical Centre, Wilhelmina Children's Hospital, in Utrecht (n=11). The donors originated from the national donor registry of the Europdonor Foundation, International donor registries or were related individuals. The follow up data was obtained from the Dutch national transplantation registry Typhon. The median follow-up of all patients was 1 year (0.1 - 10 years). The median follow-up of the surviving patients was 4 years (1 - 10 years).

In our centre the CTLp assay is routinely used as a tool to select the most suitable stem cell donor for a patient. However, we had to exclude 21 couples for which the CTLp assay could not be performed due to an insufficient number of available donor or recipient peripheral blood lymphocytes (PBL) (n = 8) or because the test failed (n = 13).

Diagnosis at time of transplantation, age of recipients and donors, cytomegalovirus (CMV) serology, preconditioning and Graft versus Host Disease (GVHD) prophylaxis of the 53 included pairs are shown in table 1. The following diagnoses were categorized as conditions with a high risk for transplant related mortality: acute lymphocytic leukaemia (ALL) or acute myelogeneous leukaemia (AML) beyond first remission or in relapse; chronic myelogeneous leukaemia (CML) in second chronic phase, accelerated phase or in blast phase; severe aplastic anaemia (SAA), Fanconi anaemia (FA), and myelodysplastic syndrome (MDS).

HLA typing and donors/recipient matching

The donors and recipients were typed at high resolution for the loci HLA-A, -B, -C, DRB1, DQB1 and DPB1 as described before.[20] The following techniques were used: the polymerase chain reaction sequence specific primer (PCR-SSP) for high resolution allele typing and sequence based typing (SBT) for part of the HLA-C alleles. All pairs had a single HLA-A, -B or -C antigen/allele mismatch in the graft-versus-host direction; 19 were mismatched for HLA-A, 6 for HLA-B and 28 for HLA-C (Table 1). All pairs were matched for the HLA-DRB1 and -DQB1 alleles.

Amino acid sequencing of the mismatched MHC class I molecules.

The amino acid sequences were obtained from the website of the European Bioinformatics Institute (http://www.ebi.ac.uk/imgt/hla/). The mismatched MHC molecules were examined for amino acid differences (substitutions) on the α1 and α2 domain (positions 1-182). The $\geq 5\alpha 5\beta$ MHC class I mismatches were defined as having at least five amino acid differences in the α helices plus at least five in the β sheet. The β helices of MHC class I consist of

positions 50-85 and 138-179 and the β sheet of MHC class I is determined by positions 4-12, 21-28, 32-37, 94-102, 112-118 and 123-126. This definition is based on our previous work where we observed that single MHC class I mismatches falling into the ≥5α5β category were associated with an undetectable T cell alloreactivity in the CTLp assay.[7]

Cytotoxic T-Lymphocyte precursor assay

The CTLp assay was performed as described by Zhang *et al* and Oudshoorn *et al*.[20,21] The target cells were labelled with ^{51}Cr. The reproducibility of this assay has been described previously.[21] Each assay was performed in the graft-versus-host (GVH) direction; i.e. donor cells were used as the responder and the recipient cells as the stimulator and target. Cultures showing higher lysis than three standard deviations above the mean of the spontaneous release (target cells without any responder cells) were considered to be positive. The frequency of CTLp and 95% confidence interval were calculated as described by Taswell et al.[22-24] Only those experiments, which showed $p > 0.05$ using the jack-knife method were accepted. Thus the relationship between responder cell dose and the number of nonresponding wells was considered to be consistent with a single-hit kinetic model. The CTLp assay was defined negative if the CTLp frequency was ≤ 1 per 10^6 PBL and positive if the CTLp frequency was > 1 per 10^6 PBL.

Inhibitory KIR ligands

Besides cytotoxic T cells, natural killer (NK) cells are thought to be possibly involved in killing of the host cells. NK cell reactivity can be inhibited by specific inhibitory killer immunoglobulin-like receptor (KIR) ligands.[25] HLA-B molecules bearing the HLA-Bw4 motif are ligands for inhibitory KIR, while those bearing the HLA-Bw6 motif are not. HLA-C molecules bearing the Ser77 and Asn80 motif (C1) are ligands for the inhibitory KIR2DL2 and KIR2DL3 while HLA-C molecules bearing the Asn77 and Lys80 motif (C2) are ligands for the inhibitory KIR2DL1.[26,27] NK cell mediated alloreactivity can occur when the target cells do not have the same inhibitory motifs as the responder.[28]

Conditioning regimen and transplantation

Conditioning therapy prior to stem cell transplantation consisted of total body irradiation (TBI) in combination of Cyclophosphamide in 34 cases or, a combination of Busulfan & Cyclophosphamide in 15 cases. Four patients received non-myeloablative conditioning therapy, either TBI and Fludarabine (n = 1), or Beam (n = 3). Cyclosporine was uses as GVHD prophylaxis in 18 cases, and complemented with in vivo T cell depletion in 15 cases and methotrexate in 18 cases. Two patients received in vivo T cell depletion. The recipients were given bone marrow derived stem cells in 42 cases and peripheral blood harvest after G-CSF in 11 cases. Grafts were T cell depleted with Campath (n = 18), CD34+ selection (n = 10), or other methods (n = 16). Nine patients received non T cell depleted grafts.

Statistics

All statistical analyses were performed in SPSS 10.0. The Chi-square tests (for categorical variables) and Mann-Whitney U test (for continuous variables) were used to compare recipient-, disease- and transplantation-related variables between the groups with a positive and negative CTLp assay outcome. Overall survival after transplantation was analysed with Kaplan-Meier curves (surviving patients were censored at last contact or at time of second transplantation). Univariate and multivariate analyses were performed with the Cox Proportional Hazards Model. Other endpoints were: 1) Transplant related mortality defined as time of death without evidence of disease recurrence, 2) disease relapse defined as disease recurrence, and 3) incidence of acute (Grade II-IV) and chronic GVHD.[29-31]

Results

The patients

Overall survival in this cohort of 53 donor-recipient pairs was 44 percent after four years. HLA-A and HLA-C mismatches were well represented in this group with respectively 19 and 28 pairs, while only 6 pairs were transplanted over a HLA-B mismatch, of which all had few amino acid differences (Table 1). Fifteen pairs in this cohort were ≥5α5β mismatched. The ≥5α5β mismatched group was not predominated by HLA-C mismatches. The CTLp assay in the graft versus host direction was negative for 31 pairs and positive for 22 pairs. Of the 15 ≥5α5β mismatched pairs 12 had a negative CTLp assay outcome. Between the CTLp positive and negative group donor-recipient related parameters as gender, gender match, age and diagnosis were equally distributed, and there was no significant difference in patient conditioning and transplantation regimen parameters (Table 2a and 2b).

Table 1: Number and type of mismatched MHC class I loci

	Negative CTLp assay		Positive CTLp assay	
	≥5α5β versus not ≥5α5β		≥5α5β versus not ≥5α5β	
	(n = 12)	(n = 19)	(n = 3)	(n = 19)
Mismatch type				
HLA-A	6	2	2	9
HLA-B	-	4	-	2
HLA-C	6	13	1	8

Table 2a: Patient and donor Characteristics

	CTLp frequency in vitro		
	Negative (n = 31)	Positive (n = 22)	p value
Age mean years (range)			
Recipient	21.0 (1.4 - 62.8)	16.9 (1.2 - 46.8)	N.S.
Donor	34.9 (13.7 - 66.3)	34.1 (7.7 – 63.4)	N.S.
Recipient gender			
Male / Female	18 / 13	18 / 4	N.S.
Donor / recipient gender match			N.S.
Male / Male	11	12	
Male / Female	4	2	
Female / Female	9	2	
Female / Male	7	6	
Diagnosis			N.S.
Acute myeloid leukaemia	3	3	
Acute lymphoid leukaemia	6	6	
Other acute leukaemia	-	1	
Chronic myeloid leukaemia	6	2	
Myelodysplastic syndrome	6	4	
Lymphoma	1	1	
Non-Hodgkin Lymphoma	1	-	
Hodgkin Lymphoma	1	-	
Severe aplastic anaemia	2	2	
Fanconi Anaemia	2	-	
Multiple Myeloma	1	1	
Immune deficiency	1	1	
Other inborn errors	1	1	
Risk status of diagnosis			
Standard / high	12 / 19	8 / 14	N.S.
Patient CMV status *			N.S.
Negative / positive	19/11	10/12	

* 1 missing value

Table 2b: Treatment

	CTLp frequency in vitro		
	Negative (n = 31)	Positive (n = 22)	p value
Stem cell source			
Bone marrow / peripheral blood	26 / 5	16 / 6	N.S.
Conditioning regimen			N.S.
Myeloablative			
Cyclophosphamide & TBI	19	15	
Busulfan & Cyclophosphamide	9	6	
Non-myeloablative			
Fludarabine & TBI	1	-	
Beam	2	1	
GVHD prophylaxis			N.S.
In vivo T cell depletion & Cyclosporine	9	6	
In vivo T cell depletion	1	1	
Cyclosporine	9	9	
Cyclosporine & methotrexate	12	6	
T cell depletion of the graft			N.S.
Campath	10	8	
CD34+ selection	6	4	
Other	9	7	
None	6	3	

CTLp assay, single ≥5α5β MHC class I mismatches and survival

We observed a strong correlation between negative CTLp frequencies and overall patient survival after SCT in the single MHC class I mismatched setting (Figure 1). Four-year survival was 63 percent in case of negative CTLp frequencies and 20 percent in case of positive CTLp frequencies (hazard ratio = 2.57; 95% CI = 1.206 - 5.478; p = 0.014). Within the CTLp negative group donor-recipient pairs with a ≥5α5β mismatch demonstrated superior overall survival (Figure 2). Four-year survival was 80 percent after SCT with a ≥5α5β mismatched graft and negative CTLp frequencies (hazard ratio = 0.144; 95% CI = 0.033 - 0.633; p = 0.010), and 47 percent in case other MHC class I differences plus negative CTLp frequencies. The occurrence of acute GVHD, chronic GVHD, disease relapse and patient mortality causes are shown in Table 3. We found no statistically significant relation between the CTLp assay outcome or mismatches and these parameters (Table 4).

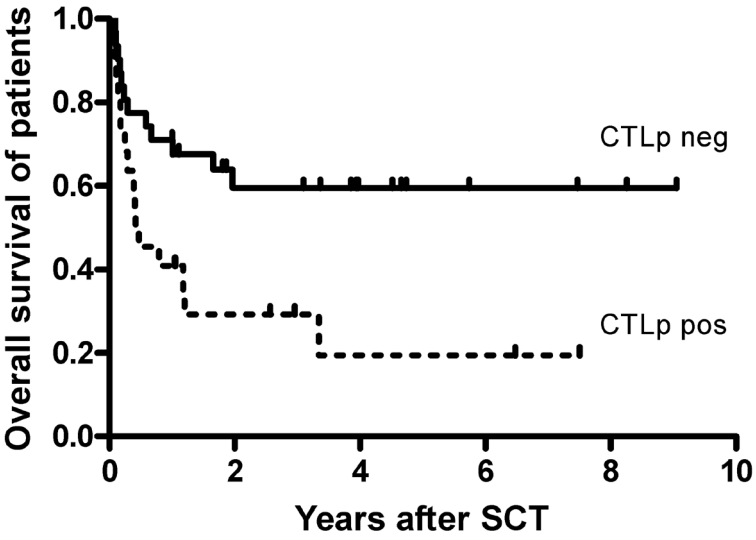

Figure 1: Overall patient survival after SCT correlated with the CTLp assay outcome. *The number of pairs in each group: 31 pairs with a negative CTLp assay and 22 pairs with a positive CTLp assay.* ***The*** *overall survival of patients correlated with the CTLp assay outcome. Positive CTLp frequencies had a hazard ratio of 2.57 (95% CI = 1.206 - 5.478; p = 0.014) compared to a* ***negative CTLp assay.***

In multivariate analysis the benefit for recipients of a ≥5α5β mismatched graft in combination with a negative CTLp assay was more apparent (Table 5). Multivariate analysis revealed a second important parameter. Transplanting a single MHC class I mismatched graft from a female donor to a male recipient had significant adverse effect on transplantation outcome independent of CTLp frequencies and MHC class I mismatch-categories. The mortality rate of this group was 11 out of 13 patients compared to 17 out of the 40 in the other group. The other parameters in the multivariate analysis, risk status of the diagnosis, CMV infection, age of the recipient and T cell depletion of the graft, did not seem to have a significant additional impact on overall survival (Table 3).

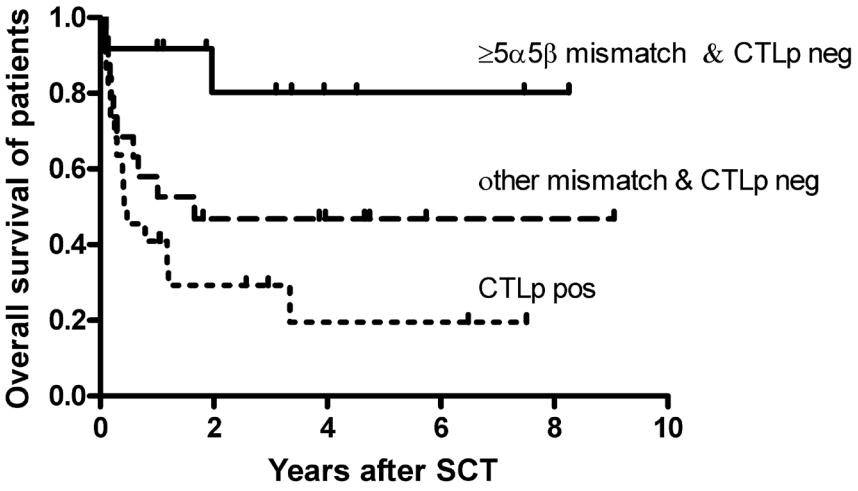

Figure 2: Overall patient survival after SCT correlated with the CTLp assay outcome and ≥5α5β mismatch category. *The number of pairs in each group: 12 pairs with a ≥5α5β MHC class I difference and* ***negative CTLp assay, 19*** *pairs with another single MHC class difference and a negative CTLp assay, and 22 pairs with a positive CTLp assay.* ***Recipients with a negative CTLp*** *assay outcome and a ≥5α5β MHC class I difference with the donor had a superior chance on survival compared to the other groups (hazard ratio = 0.144; 95% CI = (0.033 - 0.633); p = 0.010)*

Table 3: Stem cell transplantation outcomes

	CTLp neg		CTLp pos	total
	≥5α5β	other dif		
Parameter	(n = 12)	(n = 19)	(n = 22)	(n = 53)
Occurrence of GVHD				
Grade II-IV acute GVHD	1	3	2	6
Chronic GVHD	3	4	3	10
Relapse	4	4	7	15
Cause of death				
Relapse-related mortality		4	6	10
Transplant-related mortality	2	6	10	18

Table 4: Univariate analysis on stem cell transplantation outcomes

	Grade II-IV acute GVHD			Chronic GVHD		
Parameters	HR	95% CI	p value	HR	95% CI	p value
CTLp freq. and mismatch			0.786			0.846
CTLp neg and ≥5α5β	0.931	(0.84 - 10.3)	0.953	1.445	(0.24 – 8.74)	0.688
CTLp neg and other dif	1.719	(0.29 - 10.3)	0.553	1.594	(0.29 – 8.82)	0.593

	Relapse		
	HR	95% CI	p value
CTLp freq. and mismatch			0.407
CTLp neg and ≥5α5β	0.564	(0.16 - 1.96)	0.368
CTLp neg and other dif	0.451	(0.13 - 1.56)	0.208

	Transplant-related mortality			Relapse related mortality		
	HR	95% CI	p value	HR	95% CI	p value
CTLp freq. and mismatch			0.171			0.695
CTLp neg and ≥5α5β	0.249	(0.05 - 1.15)	0.075	0.000	(0.00 – x) **	0.394
CTLp neg and other dif	0.584	(0.21 - 1.61)	0.299	0.574	(0.16 - 2.06)	0.962

*Hazard Ratio (HR) ** Due to no occurrence of relapse related mortality in the "CTLp neg and ≥5α5β" group, coefficients did not converge and no models could be fitted.

Table 5: Results from multivariate analysis on patient survival after SCT

Parameter	Hazard ratio	95% CI	p value
CTLp frequency and mismatch			**0.027**
CTLp neg. and ≥5α5β	**0.133**	**(0.03 - 0.61)**	**0.009**
CTLp neg. and other dif	0.618	(0.26 - 1.50)	0.29
Female donor & Male patient	**3.060**	**(1.38 - 6.77)**	**0.006**
High risk diagnosis	1.133	(0.49 - 2.60)	0.77
Patient CMV status positive	1.209	(0.53 - 2.74)	0.65
Age of the patient at SCT	1.006	(0.98 - 1.03)	0.66
T cell depletion of the graft	1.109	(0.42 - 2.90)	0.83

MHC class I mismatch-categories and survival

Irrespectively of the CTLp assay outcome, four year overall survival of recipients of a ≥5α5β mismatched graft was 65 percent compared to 37 percent of recipients of another MHC class I mismatched graft (Figure 3). This was not statistically significant (hazard ratio = 0.440; 95% CI = 0.167-1.160; p = 0.1). In multivariate analyses, however, there was a significant correlation. The ≥5α5β mismatch had a 0.316 hazard ratio (95% CI = 0.16 - 0.81; p = 0.014) on overall patient survival. Transplanting a graft from a female donor to a male recipient had a 3.408 hazard ratio (95% CI: 1.53-7.68; p = 0.003), while risk status of the diagnosis had a 1.150 hazard ratio (95% CI: 0.49 - 2.70;p = 0.8), CMV infection had a 1.343(95% CI = 0.60 - 2.99; p = 0.5), age of the recipient had a 1.002 hazard ratio (95% CI: 0.98 - 1.03; p = 0.9) and T cell depletion of the graft had a 1.361 hazard ratio (95% CI: 0.54 - 3.45; p = 0.5). The CTLp frequencies were not included in this multivariate analysis because they are related parameters.[7]Overall survival of the 21 pairs excluded from this study was 40% after four years, which is similar to the pairs included within this study. Nine pairs had a ≥5α5β mismatch. There was a trend toward better survival for ≥5α5β mismatched pairs; data not shown.

Mismatched inhibitory KIR ligands on HLA-C

None of the HLA-B mismatched pairs had an inhibitory KIR ligand mismatch. Five HLA-C mismatched pairs had an inhibitory KIR ligand mismatch. Within the HLA-C mismatched group we did not find a relation between inhibitory KIR ligand mismatches and four year overall patient survival. Two out of five patients with an inhibitory KIR ligand mismatch survived compared to nine out of 23 inhibitory KIR ligand mismatched patients. Three KIR mismatched pairs were ≥5α5β mismatched, of which two survived. The two other KIR mismatched pairs were not ≥5α5β mismatched and both died.

Discussion

In the present report, we demonstrate the prognostic value of the CTLp assay for the outcome transplantation with single MHC class I mismatched grafts. In agreement with earlier studies, positive CTLp frequencies are associated with a strong adverse effect on SCT outcome in comparison to negative CTLp frequencies.[8-13] A significant number of transplantations with negative CTLp frequencies, however, also lead to poor outcome. Combining the MHC sequence difference categories with the in vitro CTLp results proved to be more informative and appears to enhance the predictability of SCT outcome. A single ≥5α5β MHC class I mismatch in addition to a negative CTLp frequency was associated with superior survival after SCT, compared to other single MHC differences. No significant effect on the occurrence of GVHD and relapse were observed, which may be explained by the application of T-cell

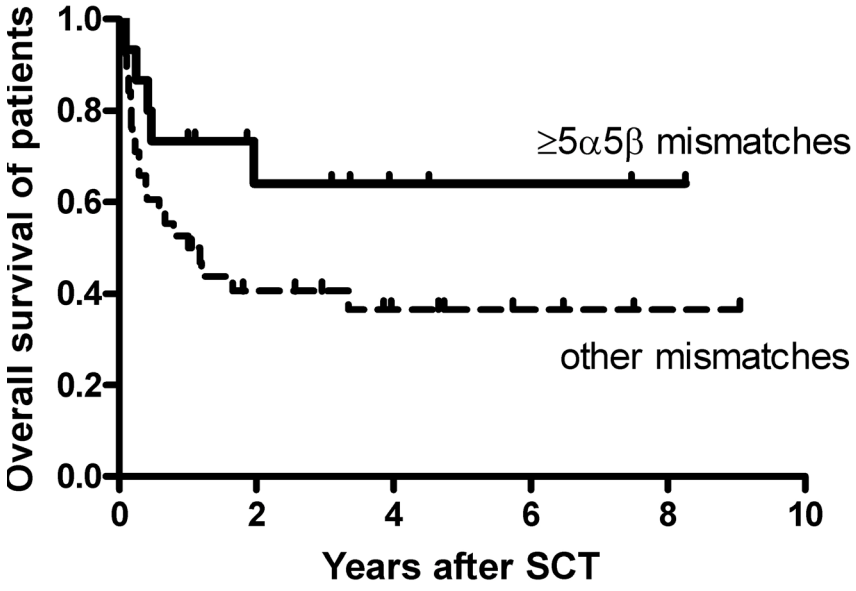

Figure 3: Overall survival of patients related to ≥5α5β MHC class I mismatch. *The number of pairs in each group: 15 pairs with a ≥5α5β MHC class I difference, 38 pairs with another single MHC class difference. The results were not statistically significant (hazard ratio = 0.440; 95% CI = 0.167-1.160; p = 0.1).*

depletion as well as the relatively low incidence of these endpoints. Comparison between the negative CTLp assay and ≥5α5β category shows that the prognostic value of the ≥5α5β MHC class I mismatch is similar to that of the CTLp assay. Four year overall survival was 63 percent in case of a negative CTLp assay and 65 percent in case of a ≥5α5β mismatched graft, which is not significant. In addition, survival was 20 % for CTLp-positive patients and 37 % for patients with another mismatch. The ≥5α5β category, however, is a less laborious than the CTLp assay. But considering our results we are of opinion that additional in vitro testing is important when using the ≥5α5β category.

Our findings seem in contradiction with the widely propagated idea that MHC mismatches with few amino acid sequence differences are more advantageous in SCT than mismatches with more sequence differences.[5,6,32] An upper limit to the degree of MHC sequence disparity still able to elicit an allogeneic CTL response however, does not exclude a lower limit of allorecognition. A problem which could arise in some cases is that a ≥5α5β mismatched MHC class I molecule could lead to deficient recognition of pathogenic antigens; something less likely to occur in case of few amino cid sequence differences. However, in the case of single class I mismatched donor recipient pairs the matched class I molecules can probably fulfill this task.

Although alloreactive CTL are considered to be responsible for SCT related clinical complications, NK cells are also able to lyse allogeneic cells. Highly diverged MHC class I mismatches as ≥5α5β are more likely to be KIR ligand mismatched and thus could elicit NK responses. We however did not find a relation between inhibitory KIR ligand mismatches and survival. Having a ≥5α5β mismatch next to an inhibitory KIR ligand mismatch did not seem to decrease the chances on patient survival after SCT. The role of alloreactive NK cells in SCT, however remains a controversial subject as it has been described to be both unfavourable and beneficial for successful SCT outcome.[33-39]

In our patient cohort a ≥5α5β effect had a greater impact on recipient survival than most of the other factors such as age of the recipient, high risk status of the haematological disorder, CMV infection, and T cell depletion of the graft which all have been described to influence successful SCT outcome.[40-42] We could confirm the adverse effect of the female donor male recipient combination.[43] Selection of such a single MHC class I mismatched female donor instead of selecting a male donor with a similar HLA mismatch cannot be recommended. This parameter affecting SCT outcome did not correlate with in vitro CTL alloreactivity before transplantation. The absence of such an association may be explained by the hypothesis that not all peptides presented by MHC class I in the recipient are also presented by the peripheral blood lymphocytes in the CTLp assay. Another possibility is that it is depending on other cell types of the immune system. However, many studies have described the significance of the cytotoxic T cell response against male minor histocompatibility antigens presented by either matched or mismatched recipient MHC.[44-47]

A multi centre and multivariate analysis of stem cell transplantation following the criteria presented here will elucidate the threshold of sequence differences that do not elicit T cell alloreactivity. It might be suitable to include structural data on MHC molecules and functional similarity of amino acids.

In conclusion, the present analysis demonstrates that there is an upper threshold to the sequence differences of MHC class I mismatches that lead to T cell alloreactivity and poor SCT outcome. Provided that the graft is single MHC class I mismatched, a highly diverged MHC class I mismatch can be permissible for transplantation and thus lead to successful SCT outcome; information obtained from in vitro analysis however remains imperative. This option of acceptable mismatches for SCT generates a larger pool of potentially compatible stem cell donors for patients lacking a fully MHC matched donor. Especially because donors with single highly diverged MHC mismatches are more available in the worldwide donor pool than those with only a small MHC disparity.

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