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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The *HistoCheck* algorithm does not predict T cell alloreactivity in vitro.

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Not my way

The HistoCheck algorithm does not predict T cell alloreactivity in vitro.

A major problem in unrelated haematopoietic stem cell transplantation is the development of graft versus host disease. This is caused primarily by donor T lymphocytes recognizing allogeneic major histocompatibility complex (MHC) antigens on tissues of the recipient, leading to the destruction of these tissues. Elsner and co-workers proposed a sequence-similarity matching (SSM) score for MHC incompatibilities to predict alloreactivity using structural data on MHC molecules and functional similarity of amino acids.[1,2] The emphasis lies on amino acid positions involved in MHC peptide binding or those important for recognition by T cell receptors. A high SSM score represents high dissimilarity between MHC molecules and should correlate with high T cell alloreactivity. An Internet based software tool, called *HistoCheck*, was developed to assess the SSM score between a pair of MHC class I or class II alleles (www.histocheck.de).

We tested the usefulness of the SSM score in predicting T cell alloreactivity in vitro in a single MHC class I allele mismatched setting to consider the possibility to replace the cytotoxic T-lymphocyte precursor (CTLp) test with the SSM score. In our centre T cell alloreactivity is measured with a cytotoxic T-lymphocyte precursor (CTLp) assay as described by Zhang et al and Oudshoorn et al. [3,4] We routinely use this assay as a tool for selecting the most suitable stem cell donor as several studies and our own experience show that the CTLp assay can predict stem cell transplantation outcome.[5-8]

We retrospectively analysed 74 allogeneic haematopoietic stem cell donor/patient pairs for whom a CTLp assay has been performed during the donor search. The pairs had been typed at high resolution for HLA-A, -B, -C, -DRB1, -DQB1 and -DPB1. All had a single HLA-A, -B or -C mismatch in the graft versus host direction and were HLA-DRB1 and -DQB1 allele matched; 26 were mismatched for HLA-A (20 antigen mismatches / 6 allele mismatches), 9 for HLA-B (1 antigen mismatch / 8 allele mismatches) and 39 for HLA-C (all antigen mismatches). The SSM score of the MHC class I incompatibilities were computed with *HistoCheck*.

We compared the SSM scores between the pairs with a clearly detectable CTLp frequency (CTLp > 5 per 10^6 peripheral blood lymphocytes (PBL)) and no detectable CTLp frequency (CTLp ≤ 1 per 10^6 PBL). No clear-cut relationship between T cell alloreactivity in vitro against single MHC class I mismatched PBL and the SSM score was seen (fig 1 and 2). MHC class I mismatches with high or low SSM scores can lead to detectable and undetectable CTLp frequencies.

Thirty-nine donor/patient pairs reached transplantation of which 21 had SSM scores above ten. Only ten cases had detectable CTLp frequencies in vitro. This cohort had a low incidence of graft versus host disease (GVHD), due to GVHD prevention protocols. There were five cases of acute GVHD grade II-IV and eight cases of chronic GVHD. There was no obvious relation between the incidence of acute or chronic GVHD and SSM scores or CTLp

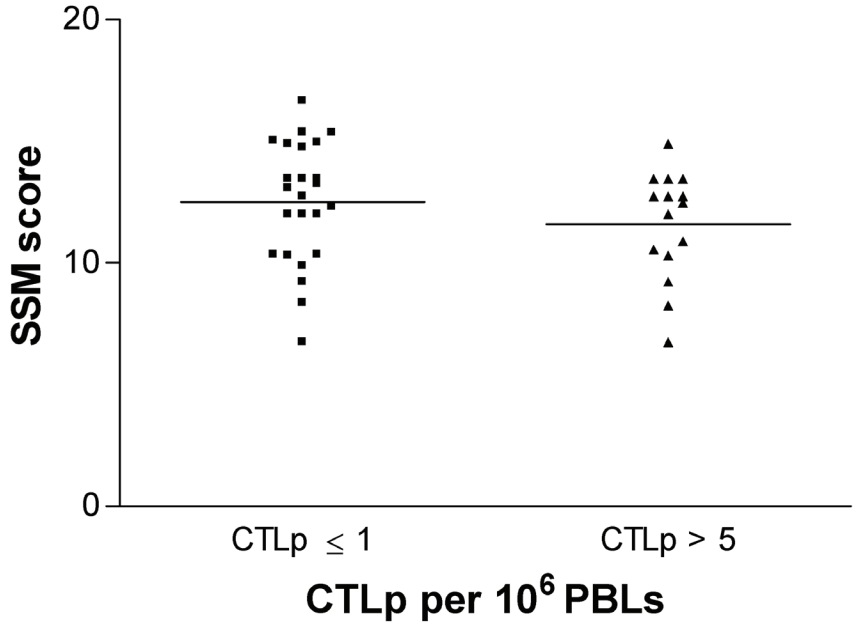

Figure 1. The relation between the SSM score of donor/patient couples with a single HLA-A or -B allele mismatch and T cell alloreactivity in vitro (CTLp/10^6 PBL). *The number of pairs in each group: 12 within the group with an undetectable CTLp frequency and 23 within the group with detectable CTLp frequency. Horizontal lines indicate the mean of each group. No difference was found for HLA-A and -B mismatches (p = 0.54).*

frequencies in vitro. The overall survival in this small cohort was 51% (median = 4.2 years, range = 1.8 –10.1 years). The Cox proportional hazard model demonstrated that the CTLp assay was more likely to be prognostic for overall survival than HistoCheck. Detectable CTLp frequencies increased the hazard (hazard ratio = 2.24; p=0.098) in contrast to the SSM score (hazard ratio = 0.94; p= 0.997).

These results are in agreement with those from Shaw and colleagues.[9] They did not find obvious benefits for patients who received haematopoietic stem cell transplants from HLA mismatched donors with low SSM scores.

Our previous study showed that in a substantial number of cases, class I MHC molecules with numerous sequence differences on both the α helices and the β sheet did not elicit an allogeneic CTL response.[10] These combinations naturally have high SSM scores. We hypothesise that thymic selection may be the reason for the lack of T cell alloreactivity

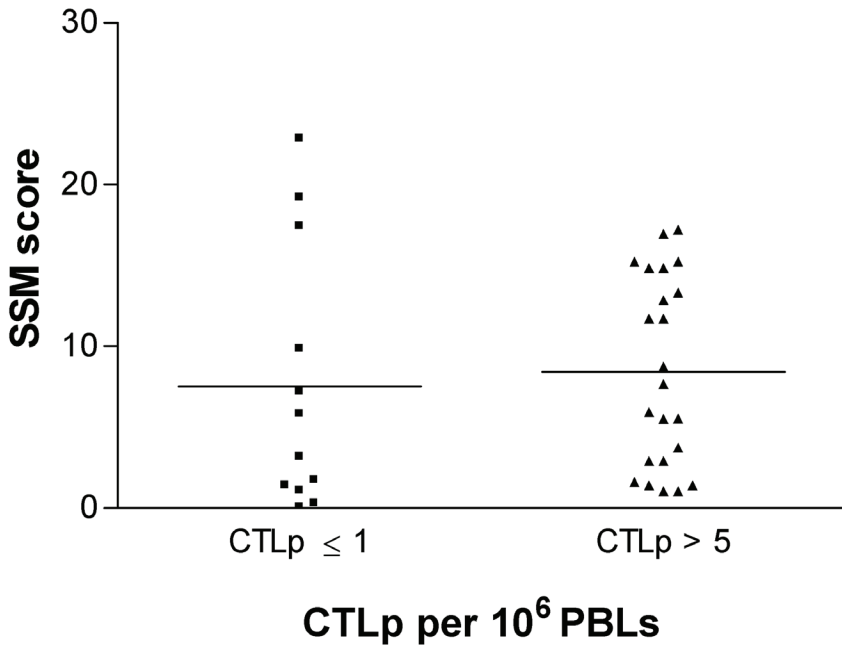

Figure 2. The relation between the SSM score of donor/patient couples with a single HLA-C allele mismatch and T cell alloreactivity in vitro (CTLp/10^6 PBL). *The number of pairs in each group: 24 within the group with an undetectable CTLp frequency and 15 within the group with detectable CTLp frequency. Horizontal lines indicate the mean of each group. No difference was found for HLA-C mismatches (p = 0.27).*

in vitro in case of mismatched MHC class I molecules with numerous sequence differences. T cells with a high affinity for very dissimilar MHC probably have not enough affinity for self-MHC and are not positively selected. The post selection T cell repertoire of an individual would therefore not associate with MHC molecules with too many amino-acid differences. It is therefore unlikely that the SSM score is suitable for haematopoietic stem cell donor selection.

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