Bone Marrow and Peripheral Blood Stem Cell Transplant: A Bioinformatics Approach for Mismatched Donor Recipient Pairs

Hamid Nawaz Tipu

ABSTRACT
Bone marrow and peripheral blood stem cell transplants when performed outside the family require high resolution matching of donor and recipient for human leukocyte antigen loci. Marrow registries like National Marrow Development Program in developed countries maintain record of donors and provide most suitable donor when a recipient needs a transplant. Being outside families and due to lack of shared haplotypes, these are not fully matched. Depending upon condition of patient and time available, several times one or two loci mismatched marrow has to be transplanted. This matching can be further enhanced by introduction of a recently introduced branch of science known as Bioinformatics. Combining the knowledge of computer softwares and transplant biology, it is possible to place any protein (in this case specific human leukocyte antigen alleles of potential donors and recipient) against any other, for exact amino-acids match/mismatch in user defined region and thus choosing the better-matched donor. In this write-up, an introduction of few programs available that can be used for the said purpose is given with a brief discussion of approach already used by other scientists.

Key Words: Bone marrow and peripheral blood stem cell transplant. Human leukocyte antigen. Bioinformatics.

Need for Transplant Registries: Bone marrow transplant (BMT)/Peripheral Blood Stem Cell (PBSC) across Human Leukocyte Antigen (HLA) barrier poses a significant restriction to successful transplant outcome. In the USA and other developed countries, this problem is circumvented through maintenance of HLA registries of potential donors, for example, in National Marrow Donor Program (NMDP) and Bone Marrow Donors Worldwide (BMDW) that offer a suitable match to patients requiring transplant. This is required as only about 30% of patients can get an HLA matched donor within the family, rest 70% have to depend upon donors outside family,1 which also significantly reduces the chance of a full match.

In third world countries or where no such registries are operating, transplants are usually not carried out beyond family members thus limiting the number of potential donors. HLA matching when done at high resolution leaves little doubt of a match/mismatch but in routine low/intermediate resolution typing is performed which is unable to discriminate specific alleles.2 This might not be an issue due to shared haplotypes if donor and recipient are related but in unrelated cases, intermediate to low resolution typing due to shared haplotype may prove misleading. This requires formation of a similar registry at national level, the working of which is proposed in a similar manner as that of other worldwide registries are operated. Such registries store HLA type of potential donors in databases through a network of affiliated hospitals and blood banks. Whenever, a patient requires BMT/PBSC, his HLA type is submitted to registry and screened for suitable donor which if matched is further asked to donate. This clearly increases the number of suitable donors available, as NMDP has facilitated transplant of over 55,000 patients worldwide beyond families.

HLA matching between donor and recipient: Currently NMDP recommends that donor and recipient must be tested at HLA A, B, C and DRβ1.3 Transplantations are usually not carried out under 6/8 loci match for adult donors.4 Individual transplant centers may have different matching requirements. HLA molecule functions to present self and foreign antigens (peptides) to T-lymphocytes.5 These peptides bind to pockets in peptide binding groove of HLA molecule. HLA class-I molecule is composed of α 1,2, and 3 domains and a β2 microglobulin, with α1 and α2 each forming one α helix and four β sheets of peptide binding groove. Similarly, HLA class-II molecule is composed of two α and two β domains with α1 and β1 each forming one α helix and four β sheets of peptide binding groove (Figure 1).6 The amino-acids at peptide binding positions of HLA molecule are critical in determining whether a specific HLA molecule will bind a specific peptide or not, and in
fact, this interaction forms the basis of foreign antigen presentation to T-lymphocytes in transplant rejection as well as auto-antigen presentation in autoimmune disorders.7

Since different HLA alleles differ in their amino-acid sequence at peptide binding groove also, these have variable affinity and thus variable presentation for various peptides. So what if an otherwise mismatched pair at a single locus or two is screened for such a donor whose peptide binding groove amino-acids are the same as those of donor, despite different alleles? That means although alleles and thus amino-acids sequence will differ but only in regions not associated with peptide binding and hence will not be expected to elicit rejection. The converse of it might be true also, that some recipients who have already received a mismatched transplant do well while others do not. Its answer also lies in same proposition. In fact same approach has been utilized by several researchers. Kawase et al. identified non-permissive allele mismatch combinations (four HLA-A, one HLA-B, seven HLA-C, one HLA-DR and two HLA-DP) for severe acute graft versus host disease (aGVHD).8 They further analyzed the amino-acid substitutions in donor mismatched pairs and impact on aGVHD. Pidala et al. have analyzed the specific amino-acid substitutions at peptide binding pocket of HLA molecule in donor recipient pairs and determined its effect on GvHD and transplant related mortality (TRM).9 Marino et al. have analyzed 389 amino-acid substitutions at 127 positions in 2107 donor recipient pairs and identified 33 substitutions as predictors of death at day 100 post-transplant.10

Role of bioinformatics: Related donor recipient pair matched with high resolution HLA typing does not require any additional matching.

Unrelated donors mismatched with recipient at one or two loci should be compared with recipient (at the unmatched loci only, after high resolution HLA typing) for amino-acid mismatches, especially at peptide binding site. The most suitable donor available can be chosen based on no/minimum amino-acid mismatches, especially emphasizing upon already established permissive/non-permissive, matches/mismatches mentioned in literature referenced above. There are several databases that maintain updated information about HLA alleles. Few most commonly employed (and their link for accessing HLA databases) include National Center for Biotechnology Information (NCBI), http://www.ncbi.nlm.nih.gov/projects/gv/mhc/main.fcgi?cmd=init, European Molecular Biology Laboratory-European Bioinformatics Institute (EMBL-EBI), http://www.ebi.ac.uk/ipd/imgt/hla/allele.html and HLA Nomenclature, http://hla.alleles.org/alleles/index.html. These databases contain detailed information about individual HLA alleles, including their genomic sequence, protein sequence, Single Nucleotide Polymorphisms (SNPs) etc, and enable researcher to analyze introns, exons, untranslated regions etc. Additionally, viewer can analyze his molecule in 3-dimensions to view all chains, even at atomic level and comparing two molecules in 3D, but that would be beyond the scope of this review.

Being restricted to linear amino-acid sequence comparison for HLA typing, it is easy to compare two alleles for any needed feature including amino-acids sequences. It is even possible to analyze the differences for individual exons/introns as routinely HLA typing accounts for polymorphisms only in exon 2 and 3 for HLA class-I and exon 2 for HLA class-II. Figure 2 shows snapshot of amino-acid sequence comparison of two HLA-A alleles at exon 2.

Figure 1: Peptide Binding Groove of HLA molecule showing α helices at sides and β sheets at bottom (modified from protein data bank, PDB ID 415B).

Figure 2: Amino-acid sequence comparison of two HLA-A alleles at exon 2.
CONCLUSION

It is suggested that maintaining the central record of donors is an essential step towards increasing the number of potential donors available. When a recipient needs, this record can be screened for best possible donors available. Although sufficient data in this regard is still lacking but under unavoidable circumstances, using bioinformatics approach, most suitable donor can be selected among few available, that is likely to reduce rejection rates.

REFERENCES


