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Session : Postgraduate Course 9 (Laboratory)

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Session Title : Transplant Immunology: Practical issues in HLA Eplets and Desensitization Monitoring

Desensitization for HLA incompatible transplantation

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Within the continuously growing waitlist for organ transplantation, up to one-third of the candidates are considered 'highly sensitized'. Desensitization offers a chance to overcome the barriers of transplantation, thereby expanding the possibility of proceeding with transplantation. The process of HLA incompatible transplantation is complicated and requires a well-defined management strategy comprising of several essential elements. These components include a dedicated team of willing physicians/surgeons, specialized expertise in histocompatibility laboratory practices and an extensive medical resource allocated for post-transplant monitoring, not necessarily in the order of their importance. It is worth noticing that the process of HLA incompatible transplantation is not for the faint hearted as success is never guaranteed. Nonetheless, with clearly defined objectives and strategic approaches using HLA incompatible transplantation 'program', favorable outcome can be carefully anticipated. Probably the most pivotal aspect is how we define incompatibility. There 'was' an era when complement dependent cytotoxicity (CDC) crossmatch positivity was considered an absolute contraindication for transplantation. When a donor-recipient pair is deemed incompatible, it is important to define the level of incompatibility at methodological level, such as CDC or flow cytometry, single antigen bead or C1q, and specify the degree of incompatibility in terms of titer and/or MFI cutoffs. Individuals with high cPRA (or %PRA) are often considered categorically as 'highly sensitized', although their antibody profiles with regards to antigen specificity and strength can be unique. The goals of the desensitization program must be clearly defined before proceeding with transplantation, even when employing adjuvant immunosuppression. The absolute contraindication of the past has been breached by modern desensitization protocols. Delving into the details of HLA antibody testing, it is important to acknowledge the limitations of the assay and what we can do to improve the accuracy. In addition to false positivity caused by denatured HLA antigens, sera from highly sensitized patients can be troubled by prozone phenomenon and high background reactivities. Any available ancillary information, such as recipient/donor typing, previous transplant, sensitization history (pregnancy, transfusion, medication, vaccination, etc.), previous crossmatch results can significantly aid interpretation. Common laboratory practices, such as serum pretreatment involving DTT, EDTA, heat inactivation, and serum

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dilutions, should be duly considered. A significant laboratory concern regarding HLA incompatible transplantation involves the impact of pharmaceutical agents used during desensitization. Highly sensitized patients often receive anti-CD20, proteasome inhibition, IVIG treatment and extensive cycles of therapeutic plasma exchanges. These desensitization methods can significantly affect HLA antibody testing results, and laboratories must be keenly aware of these effects. It is critical to distinguish between false positivity and the ongoing incompatibility to make confident, informed clinical decisions. Furthermore, even in cases where absence of HLA antibodies and a negative crossmatch have been confirmed, non-HLA antibodies causing antibody-mediated rejection shortly after transplantation are confused with false negative results. The laboratories should remain cognitive of such scenarios and be equipped with options to provide prompt resolutions. In addition to detailed interpretation of testing, incessant accessibility to laboratory support is equally important, as many therapeutic decisions depend on the prompt laboratory results. A proficient HLA laboratory should be capable of offering antibody monitoring services throughout the desensitization program, including within-day monitoring and urgent post-transplantation assessments. The purpose of testing the sera is not only to detect the presence of HLA antibodies, but the expertise of the lab should also allow for detection of clinically relevant HLA antibodies. This discussion delves into the review of several successful desensitization protocols, examining their common components and how laboratory considerations are integrated into these programs. Additionally, we briefly touch upon upcoming issues in the latest desensitization protocols, such as the use of IdeS (imlifidase).