Implementing Virtual Crossmatch in Australia

Summary

A physical complement-dependent cytotoxicity crossmatch (CDC) has been standard clinical practice prior to transplantation from deceased donors in Australia. The CDC is intended to exclude the presence of strong donor-specific antibodies (DSA) against human leucocyte antigens (HLA). However, CDC has limited sensitivity and specificity and is no longer routinely utilised in most transplant programmes worldwide. Moreover, the equipment and reagents to perform CDC have become increasingly difficult to source, and it is likely that there will be a critical shortage of consumables within 12-18 months.

Virtual crossmatch (VXM) uses detailed information about the anti-HLA antibody profile of recipients combined with comprehensive HLA typing of the donor to assess histocompatibility without a pre-transplant CDC. VXM significantly reduces the workload for compatibility assessment and reduces the time for generation of organ allocation lists, potentially reducing cold ischaemic times. VXM has been successfully implemented internationally and OrganMatch has been configured to facilitate the transition to VXM. This document provides a brief summary of the plan to introduce VXM in Australia.

Background

In the early era of transplantation, DSA were a major problem for sensitised transplant recipients. At this time, the capacity to identify DSA and to define donor HLA was limited, and as a result, organs could be inadvertently transplanted in the presence of strong DSA, often failing immediately due to hyperacute rejection. In 1969, Paul Terasaki described the use of the CDC assay, which revolutionised transplantation practice by allowing identification of strong DSA prior to transplantation.

Since then, technological advances have dramatically improved the accuracy of immunological risk assessment before transplantation. Firstly, donor HLA type is now defined for all HLA loci prior to transplant allocation. Secondly, serum from patients awaiting transplantation is screened for anti-HLA antibodies using solid phase assays (the 'Luminex' assay). These assays provide a vastly more detailed analysis of sensitisation than was possible previously. Combining these data in a VXM allows a highly accurate assessment of transplant compatibility, permitting transplantation to proceed in the majority of cases without a physical crossmatch. In certain situations where a physical crossmatch is judged necessary at the time of transplantation, most centres internationally would now use a flow crossmatch (FXM), which provides greater sensitivity than CDC.

Current practice

Patients waiting for a transplant are typically screened for anti-HLA antibodies using a solid phase assay at least annually, and as frequently as every three months in some transplant programmes. Potential DSA identified can be listed as unacceptable antigens in OrganMatch – hence we already use the process of VXM to exclude some potential organ offers in Australia. In addition, sera collected every 1-2 months are used to perform a physical CDC prior to transplantation.

With the increased effectiveness of pre-transplant DSA screening, unexpected positive CDC crossmatches at the time of organ allocation have become rare events. When they do occur, further investigation typically identifies these as false positive results generated by IgM antibodies that are not clinically important.

Proposed changes with introduction of VXM

Pre-transplant

With the transition to VXM, it will be necessary to increase the frequency of solid phase antibody screening for patients on transplant waiting lists to minimise the chance of overlooking clinically significant sensitisation. It will be even more important for clinicians to report any potential sensitising events so that additional antibody screening can be performed.

For many patients without sensitisation, the risk of omitting CDC will be negligible. However, the situation will be more complicated for highly sensitised patients. Transplant clinicians will need to work in collaboration with the tissue typing laboratory to define acceptable/unacceptable antigens for these complex patients.

At the time of organ offer

A significant benefit of moving to VXM will be the opportunity to reduce cold ischaemic time, as most organ offers will be able to proceed without waiting for a physical crossmatch result. For certain recipients (for instance where a potential DSA has been identified) the risk of omitting a physical crossmatch may be higher and therefore in selected circumstances an FXM pre-transplant could assist in defining immunological risk. Since it will only be feasible to perform a small number of FXM for a particular deceased donor, good communication between clinicians, donor coordinators and tissue typing laboratories will be needed to allow timely identification of recipients who require a pre-transplant FXM.

Conclusion

The transition to VXM will occur in 2021 and will have important implications for the work of donation and transplant professionals in Australia. A working group has been established by TSANZ with support from OTA and will liaise with clinicians and tissue typing scientists from across the sector so that we can continue to deliver safe and high-quality transplantation practice in Australia.

A/Prof Ross Francis
Chair, VXM Working Group