Highly Sensitised Patients undergoing Cardiac Transplantation

Highly sensitised patients are generally those who have had previous cardiac surgeries which have involved foreign matter eg grafts, valves and/or blood transfusions. Antibodies are formed to this foreign material making these patients more susceptible to humoral / vascular rejection. Highly sensitised patients are those with Panel Reactive Antibody Levels in excess of 10% (normal 0%). Ideally a donor should be selected to whom the recipient has no pre-formed antibodies (negative T and B-cell cross-match) or who does not have HLA antigens to which the recipient has preformed antibodies (negative virtual crossmatch), but this is frequently not realistic or achievable.

The following protocol has been compiled to allow us to transplant these highly sensitized patients in the event of a Positive T-cell crossmatch. We would also use this if a B-cell crossmatch is positive with a score <6. (The score will be documented on the crossmatch report from VTIS)

Assessment

There are various methods of evaluating for the presence of antibodies against non-self HLA.

- The Complement Dependant Cytoxicty (CDC) method is the quickest but least sensitive, and is the method used for determining the pre-transplant PRA, as well as for cross-matching at the time of transplant. It determines the presence of anti-donor HLA antibodies by complement dependent lysis of donor lymphocytes incubated with recipient serum.
    - The PRA is percentage from 0 to 100 reflecting the proportion of a pool of donor lymphocytes against which the potential recipient exhibits complement dependent cytotoxicity. A PRA > 10% indicates a sensitised potential recipient.
    - For crossmatch, the degree of cytotoxicity is graded from 0 to 8.
        - A response of 2 is considered weak, 4 is considered mild, 6 moderate and 8 severely positive.
        - Generally, a weak to mild positive B cell crossmatch is not a contraindication to transplant and doesn't require initiation of the "highly sensitised recipient" protocol.
        - A moderate or greater B cell crossmatch or positive T cell crossmatch of any degree contraindicates transplantation, except where the recipient (who usually has very high PRA levels) is explicitly and prospectively listed for crossmatch positive transplantation.
- The luminex mixed-screen assay is the most sensitive, but somewhat less specific. It measures specific antibodies against a panel of HLA antigens and is reported as positive or negative.
- The luminex single antigen assays quantify the antibody levels (MFI) against specific HLA antigens.
    - A level of < 500 is negative
    - A level of 500 - 2000 is considered weak
    - A level of 2001 – 8000 is considered moderate
    - A level > 8000 is considered strong
- Currently, Enzyme Linked Immunosorbent Assay (ELISA) has been replaced by Luminex methods in most tissue typing laboratories in Australia.

- The Luminex assays are employed in virtual crossmatching to determine the presence of and quantify donor specific antibodies. This informs the probability of a subsequent positive CDC crossmatch.
- Routinely laboratories perform tissue typing on a donor, the results of which are available in 3-5 hours, and also perform CDC based crossmatch against the potential recipient's serum, which takes 6-8 hours.
    - The earlier availability of donor typing permits "virtual crossmatch" against the recipient's known anti-HLA antibodies (from previous Luminex single-antigen assay).
    - The presence of donor HLA antigens to which the recipient is known to have moderate or high levels of specific antibody predicts a subsequent positive crossmatch, and may impact on donor selection for non-urgent recipients.
- Once PRA levels exceed 20%, or the recipient has antibodies to many common HLA antigens, a negative real or virtual crossmatch is less likely and may not be feasible.
- Initiation of the highly sensitised recipient protocol rests on a positive T cell crossmatch or positive B cell crossmatch of moderate or greater severity.

Management Pre-operatively (at time of transplant)

- 3-10 mls blood in gel (brown top tube) taken for PRA levels with pre-operative bloods. This is sent to VTIS lab at Red Cross Blood Service (RCBS) Batman St, West Melbourne 03 96943590 / 3595. Transplant Coordinator will liaise with the senior scientist. This allows a more detailed retrospective assessment of the cross-match. Requires a VTIS request form. Request 'Donor-Specific Antibodies'.

Management Intra-operatively

- **Plasmapheresis** is managed by the perfusionists who would generally perform a 2-3 volume plasma exchange. A vascath will be inserted during surgery.

Management Post-operatively

- **Plasmapheresis** is required daily for day 1 through to 5, then Day 7, 9 and 11 (see Plasmapheresis for highly sensitised patients).

  Whilst the recipient is in ICU this is managed by the ICU staff. When the patient is transferred to the ward, the haemodialysis team will be involved. The process takes approx. 4 hours and can be performed on the ward, however the patient will ideally be transported in a wheelchair to the Haemodialysis unit.

- **Antibody Levels** are checked 2-3 days post-transplant and again at 5-7 days. Weekly testing is required after this.

  Luminex testing is a batched test and is usually on **Monday and Thursdays** at the lab, although if necessary these days can be negotiated with the senior scientist at VTIS. The transplant coordinator will facilitate any requests.

- **Monocloncal Antibody Induction**

  ATG Thymoglobulin (Rabbit) is required at a dose of 1.0-1.5mg/kg/day for at least 5 days.

  This medication Information sheet can be found at ATG Thymoglobulin table

- **Triple Therapy:**
  - Tacrolimus to commence on post-transplant day 2-3, when the patient is tolerating nasogastric feeds and medications. The dose is 0.1mg/kg bd. If the patient is not tolerating oral/NG medications by day 5, then the ATG can be prolonged by another 2-5 days. If intestinal function still has not returned, start cyclosporin: 1mg/kg IVI bd.
  - Mycophenolate mofetil (MMF): 600mg/m2 bd commence within 12 hours of theatre.
  - Steroids: Methylprednisolone 10mg/kg IVI for 4 doses and then 0.2mg/kgday as a maintenance dose

    See Medication table for administration

- **Intragam**

  1st Dose will be given in theatre and then again on Day 5 . Subsequent doses (if required) are required monthly for 6 months. The Transplant team will decide if therapy is to be continued. If they are an outpatient it can be done in Day Medical or along with their biopsy.

  For IVIG administrations (2g/kg) see the following link

http://www.rch.org.au/bloodtrans/about.cfm?doc_id=9219

If there is any doubt about intestinal absorption or function it is safer to continue with parenteral administration of medications.

Plasmapheresis for highly sensitised patients

Post Transplant Plasmapheresis daily for Day 1 through 5, then Day 7, Day 9 and Day 11.

The volume to be exchanged is calculated from two-thirds of the total blood volume (TBV). The TBV = 80mls/kg. For removal of antibodies a double exchange is recommended, so for a 20kg child the volume to be exchanged would be 3200mls. The maximum amount to be exchanged is 4 litres. The replacement fluid is usually 4% albumin, FFP or a combination of both.

Exchange is usually done via a vascath, this is a temporary line and IS NOT CUFFED. It is usually placed in the femoral vein. A second IV line is required for administration of drugs.

Pathology

The following pathology tests are required pre exchange:

U's& E's Cr, LFT's, FBE and diff, coagulation profile. As these pathology tests are usually done on a daily basis immediately post-op, they need not be repeated.

Replacement fluid: most commonly 4% albumin with 1-2 units of FFP at the end of therapy to minimise the risk of bleeding.

Although reactions to albumin and FFP are not common, prn orders for hydrocortisone and/or promethazine need to be written prior to the commencement of plasmapheresis.

Observations:

A full set of observations at commencement - Temperature, BP, PR and RR.

BP PR and RR to be done every 15 minutes for the first hour, then every 30 minutes until completion of the treatment. A further temperature and BP are required at completion.