NZHPA Conference Report – Roche Education Grant

Tandem Meetings – Transplantation & Cellular Therapy Meetings of ASTCT® and CIBMTR®

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With funding support from the Roche Education Grant, I was fortunate enough to attend the Tandem Transplantation and Cellular Therapy Meeting in San Antonio, Texas. This is an annual 4-day conference which ran from 21-24 February this year with over 5000 attendees. There were various track agendas which had pharmacist-relevant topics including infectious diseases, advanced practice providers, scientific and paediatric, as well as 2 full days with a dedicated pharmacy track. A draw-card to the exhibit hall was an "animal petting area" where they had kittens, puppies, rabbits and even alpacas one day, which provided a much-needed break and distraction from the intensity of the talks!

Being an American conference it is a little bit like looking in to the future with respect to treatments available overseas – one of which is gene therapy for sickle cell disease. Sickle cell disease results from mutations in the HBB gene responsible for making beta globin, a component of haemoglobin. The process of gene therapy is similar to autologous stem cell transplants and CAR-T therapy where the patient's own cells are harvested and infused back in later, following conditioning chemotherapy. After harvesting, the stem cells are modified by either gene addition, where a functional HBB gene is inserted into the stem cell, allowing for normal production of beta globin, or gene editing, where the BCL11A gene responsible for suppressing foetal haemoglobin is disrupted, allowing for increased production of foetal haemoglobin which replaces adult haemoglobin and doesn't cause cells to sickle in the same way. This process can take up to 4-6 months, and is incredibly costly – Beti-cell, Exa-cell and Lovo-cell gene therapies cost US$2.8, US$2.2 and US$3.2 million respectively!

There were a number of talks which were relevant to our current practice in NZ, and some that may be a possibility in the near future. The pharmacy track had a best practice talk from a panel of 3 pharmacists about post-transplant cyclophosphamide, a subject that is quite topical at the moment given the evidence supporting mismatched unrelated donor allogeneic stem cell transplants with PTCy as graft versus host disease prophylaxis, and current clinical trials investigating the use of PTCy following matched unrelated donor transplants as well. They discussed dosing in obese patients (with the consensus being to use IBW to calculate dose in adults), hydration and mesna regimens for prevention of haemorrhagic cystitis and future directions of PTCy including potentially decreasing the dose – the OPTIMIZE trial opened early 2023 investigating a PTCy dose of 25mg/kg on days +3 and +4 post-transplant (compared to current standard of 50mg/kg). The main questions that this study will need to answer will be whether a reduced dose of PTCy reduces the occurrence of infections in the first 100 days after transplant, and whether this reduced dose maintains the same level of protection against GVHD.

Being a pharmacist, I was naturally drawn to the advanced practice provider talk on pharmacokinetics in transplant, where a paediatric TCT pharmacist from the Memorial Sloan Kettering Cancer Centre discussed pharmacokinetic analysis of busulfan and rabbit antithymocyte globulin. Busulfan has a narrow therapeutic range, and both its myeloablative effect and toxicity (mainly VOD/SOS) are more related to the cumulative exposure to the drug rather than the dose that is given, so PK analysis/modelling is important for its safety and efficacy through transplant. There are a number of population PK models available for busulfan dosing where age and weight are the primary covariates affecting dose.

We use rabbit ATG for prophylaxis of GVHD in matched unrelated donor adult allogeneic transplants, and there is some evidence supporting the use of PK modelling for rATG in paediatric patients. Clearance of rATG is non-linear, it has a long half-life (7-14 days although the effect on lymphocytes can persist for much longer) and it exhibits wide inter-patient variability, and this may be related to the fact that rATG is cleared through binding to lymphocytes – so the absolute lymphocyte prior to rATG treatment can impact total exposure. Because of this, individualised dosing nomograms for rATG dosing in the 2022 PARACHUTE (paediatric) study

were based on patient weight and absolute lymphocyte count. rATG exposure in the days leading up to transplant (ie through conditioning chemotherapy) is important for the prevention of GVHD, and exposure in the days following transplant can impact immune reconstitution – if the exposure is too high post-transplant this has been shown to delay immune reconstitution which results in lower overall survival. Giving rATG earlier in the conditioning course should therefore optimise exposure pre-transplant and minimise exposure post-transplant – so the PARACHUTE study had rATG starting on day-9. We don't do paediatric allogeneic transplants in Wellington so I'm not sure what the standard rATG strategy is, but in adults we give on days -3 to -1 so it was interesting to hear this information about rATG PK.

There were a number of sessions discussing the impact of the gut microbiome on overall health in transplant patients, particularly in relation to GVHD. The gut microbiome and cells lining the gut can be damaged by antibiotics, chemotherapy/radiotherapy and poor diet, all of which are relevant issues for allogeneic stem cell transplant patients. Loss of mucus and weakening of the junctions between cells can lead to translocation of pathogens into the bloodstream which can activate the donor immune system leading to inflammation in the gut and GVHD. Some bacteria in the microbiome are damaging to the GI tract by breaking down mucus and interrupting this barrier. Others are protective in various ways – commensal bacteria like clostridiae provide butyrate which intestinal endothelial cells use for repair. Butyrate can also induce IL22 which stimulates Paneth cells in the gut to secrete antimicrobial peptides which form a matrix within the mucus to protect against pathogens. Paneth cells also secrete a molecule called REG3 which provides survival signals to intestinal stem cells which is essential to the regeneration of the gut. Research has shown that patients with GI GVHD have less butyrate producing bacteria in their gut, and that these patients generally also have lower gut microbiome diversity. There is ongoing research into using faecal microbiota transplants to restore the gut microbiome and the benefits of this – pioneering studies have shown that diversity of gut microbiota correlates with the occurrence of GVHD, bloodstream infections and eradication of drug resistant bacteria. There is also some evidence emerging which supports the use of FMT for steroid- and ruxolitinib-refractory GI GVHD – preliminary data has shown an overall response rate of 55% at day 28 post initiation of treatment. This treatment could have a significant impact on patients with GI GVHD, when currently we are pretty limited to treatment with steroids and (NPPA approved) ruxolitinib.

The 2025 Tandem meeting is going to be held in Honolulu, Hawaii from 12-15 February 2025. They do have a virtual programme available which makes attendance more accessible cost-wise, but who wouldn't want a trip to sunny Hawaii with some quality haematology learning in the process! I would encourage anyone working in the haematology transplant/cellular therapy setting to consider attending this conference. Thank you again to Roche and the NZHPA for the opportunity to attend this year.