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POSTER ABSTRACTS

401.BLOOD TRANSFUSION

Optimizing Immunoglobulin Replacement Therapy for Patients with B-Cell Malignancies and Hypogammaglobulinemia: The Investigator-Initiated, International, Randomized Phase II/III Rational Platform Trial, and the Rationalise (STOP IgRT) Domain

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Background & significance: Hypogammaglobulinemia is common in patients with chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma (NHL) and multiple myeloma (MM), and associated with an increased risk of serious infection. Immunoglobulin (Ig) replacement therapy (IgRT) is widely used to reduce this risk, but national guidelines and clinical practice are variable. Supportive care and treatment regimens have evolved since evidence supporting IgRT was published. Ig is expensive, in limited supply, and with increasing use of B-cell-depleting therapies in this setting, and prolonged survival, demand continues to grow globally.It is not clear when to start IgRT, nor the optimal duration or dose. Some jurisdictions require a trial of oral antibiotics (Abx) prior to starting IgRT, and some recommend a trial of stopping IgRT in stable patients. More data are needed on the benefits, risks and costs of these different approaches.
Hypothesis: For the prevention of infection in adults with hypogammaglobulinemia due to CLL, NHL or MM prophylactic oral Abx, or a strategy of patient-held emergency Abx supply only, are non-inferior to IgRT.
Study design: The RATIONAL platform trial is an investigator-initiated, international (Australia, New Zealand, Canada), phase II/III randomized controlled trial (RCT) with 3 domains:
(1) the RATIONALISE 'STOP Ig' study (ACTRN 12622000359730), now recruiting;
(2) a 'START Ig' study comparing IgRT or Abx in patients eligible to start IgRT; and
(3) a DOSE study comparing IgRT at 0.25 vs 0.4g/kg/month (m).
The platform includes qualitative, biological (immune profile, microbiome) and health economics studies.
In the RATIONALISE ('STOP Ig') domain, patients are randomized 1:1:1 to either:
- Arm A: Stop Ig and commence prophylactic oral Abx: Daily trimethoprim-sulfamethoxazole (co-trimoxazole) 160mg/800mg (doxycycline 100mg/day if co-trimoxazole hypersensitive).
- **Arm B: Stop Ig.** Keep amoxycillin/clavulanic acid 1750-2000mg/250mg and ciprofloxacin 750mg on hand for initial use for symptoms of infection, with immediate clinical review. Clindamycin 600mg if penicillin hypersensitive.
- **Arm C: Continue Ig:** IV q 4±1 wks at 0.4g/kg, modified to achieve IgG trough of at least lower limit of age-specific serum IgG reference range, OR subcutaneous (SC), dosed in line with site/country criteria.
Inclusion criteria: ≥18y with CLL, NHL or MM, receiving IgRT (IV or SC) for >6m, eligible for Ig cessation in opinion of treating clinician, life expectancy >12m, able to give informed consent and comply with each of the trial arms.
Exclusion criteria: Prior/planned allogeneic transplantation. Major infection (≥Grade 3 CTCAE v5) in preceding 3m, and/or current active infection requiring antimicrobial treatment. Already on daily Abx for purpose of preventing bacterial infection (may have antiviral, antifungal, PJP prophylaxis). Intolerance of all trial Abx options.Communication, compliance or logistics likely to limit ability to take prophylactic or emergency Abx, or obtain urgent medical attention for infection symptoms. Pregnant/breastfeeding. Creatinine clearance <30 mL/min. Splenectomy. Enrolment deemed not in patient's interest.
Primary endpoint: Event-free survival, from randomization until ≥Grade 3 infection or death from any cause. **Secondary endpoints**include other infectious outcomes to 12m, time free from hospitalization and therapeutic Abx, Abx resistance, QoL, trough Ig levels, proportion of patients who stop Ig and re-start, costs, adverse events.
End-point determination: Study is not blinded, but infections and adverse events are adjudicated by an independent, blinded outcome adjudication committee. Planned treatment duration in all arms is 12m, with follow-up via established clinical registries.
Statistical methods: STOP Ig domain has an initial cap of 300 patients and uses flexible Bayesian monitoring involving frequent interim analyses where interventions may be stopped early to declare proof-of-concept/efficacy or inferiority, or accrual may expand. Stratified by diagnosis.
Progress/Summary: This novel international platform trial will inform infection prevention strategies for the growing population of patients with CLL, NHL or MM living with hypogammaglobulinemia. The first domain ('STOP Ig') is now open at 4 sites, with the first patients recruited. To our knowledge, this is the first trial of 'stopping' Ig in this setting.

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