Haematology Research Review™

Making Education Easy

Issue 114 - 2022

In this issue:

Abbreviations used in this issue:

AE = adverse event; **ALL/CLL** = acute/chronic lymphocytic leukaemia; **ATG** = antithymocyte immunoglobulin; **BTK** = Bruton's tyrosine kinase; **Chemo** = chemotherapy; **hyper-CVAD** = hyperfractionated cyclophosphamide, vincristine, doxorubicin & dexamethasone; **IMiD** = immunomodulatory drug; **IQR** = interquartile range; **IV** = intravenous; **JAK** = Janus kinase; **PFS** = progression-free survival; **POMP** = 6-mercaptopurine, vincristine, methotrexate & prednisone; **QoL** = quality of life; **RR** = risk ratio; **TKI** = tyrosine kinase inhibitor; **VOC** = vaso-occlusive crisis.

Welcome to issue 114 of Haematology Research Review.

We begin this issue with a prospective multicentre study which assessed the safety and efficacy of orelabrutinib, a novel small molecule selective irreversible BTK-inhibitor, in patients with relapsed or refractory Waldenström's macroglobulinaemia. This is followed by an interesting phase 2 trial that investigated whether outcomes for acute lymphocytic leukaemia (ALL) were improved with the incorporation of blinatumomab into front-line therapy. The next paper reports on a systematic review and meta-analysis that explored the risk of developing second primary malignancies with the use of lenalidomide across all haematological cancer settings. We conclude this issue with the final results of the phase 2, open label, multicentre clinical trial, JeRiCHO, which explored the clinical outcomes of administering ruxolitinib, a JAK inhibitor, to patients with relapsed or refractory classical Hodgkin lymphoma.

We hope you find this update in Haematology research informative for clinical practice, and we welcome your comments and feedback.

Kind Regards,

Professor Jeff Szer AM
jeff.szer@researchreview.com.au

Evaluation of orelabrutinib monotherapy in patients with relapsed or refractory Waldenström's macroglobulinemia in a single-arm, multicenter, open-label, phase 2 study

Authors: Cao X-X et al.

Summary: The safety and efficacy of orelabrutinib, a novel small molecule selective irreversible BTK-inhibitor, in patients with relapsed or refractory Waldenström's macroglobulinaemia was assessed in this prospective multicentre study. Eligible patients (n=66) who had received ≥1 prior line of treatment were administered oral orelabrutinib 150mg/daily until unacceptable toxicity or disease progression. At a median follow-up of 16.4 months, 47 patients were examined for efficacy by the Independent Review Committee according to IWWM-6, which found a major response rate (primary endpoint) of 80.9%, with an overall response rate of 89.4%. There was a 1.9-month median time to at least a minor response, and at 12 months the PFS rate was 89.4%. Patient major response rates varied according to their genetic mutations: *MYD88L265P/CXCR4*^{S338X}-mutated 100%, *YD88L265P/CXCR4NEG*-mutated 84.6%, and *MYD88NEG/CXCR4NEG*-mutated 25.0%. The majority (91.0%) of AEs were grades 1 or 2, while neutropenia (10.6%), thrombocytopenia (6.4%) and pneumonia (4.3%) were the most common grade ≥3 AEs. Ten patients experienced serious AEs (21.3%) and there was one reported treatment-related death due to hepatitis B reactivation.

Comment: BTK inhibitors have expanded the therapeutic options for patients with Waldenström's macroglobulinaemia and this study from China looked at another member of this group, orelabrutinib, described as a selective irreversible BTK inhibitor in a multicentre phase 2 study. Patients had relapsed or refractory disease after at least one line of therapy. Forty-seven patients were assessable for response with a major response rate of over 80% at 16 months and overall response rate of almost 90%. Safety data seemed acceptable with grade 3 or higher AEs being cytopenias and pneumonia. It is not clear whether this agent will undergo further study, but initial response rates appear very encouraging.

Reference: EClinicalMedicine. 2022;52:101682
Abstract

Hyper-CVAD and sequential blinatumomab for newly diagnosed Philadelphia chromosome-negative B-cell acute lymphocytic leukaemia

Authors: Jabbour E et al.

Summary: This single-arm, single-centre phase 2 trial in Texas investigated whether outcomes for acute lymphocytic leukaemia (ALL) were improved with the incorporation of blinatumomab into front-line therapy. Eligible patients with newly diagnosed Philadelphia chromosome-negative-B-cell ALL aged ≥14 years (n=38; median age 37 years; 68% male; 55% white) were administered 4 cycles of intensive chemo (hyper-CVAD alternated with high-dose methotrexate and cytarabine) before commending 4 cycles of blinatumomab consolidation via continuous IV infusion (≤28 µg/day for 28 days every 42 days). Maintenance therapy included alternating 1 block of blinatumomab with 3 cycles of POMP chemo. The estimated 3-year relapse-free survival (primary endpoint) was 73% (95% CI 56-85) at a median follow-up of 37 months (IQR 28-49). Relapse did not occur in any patients for more than 2 years after the therapy was initiated, while a grade 3 blinatumomab-related neurological event was experienced by four patients (11%) and transient grade 3 cytokine release syndrome by one (3%). Infections were the most common non-haematological grade 3-4 AEs, which occurred in 14 (37%) and 27 (71%) of patients during the induction and consolidation chemo cycles, respectively. Treatment-related neurotoxicity led one patient to discontinue therapy, and the two deaths that occurred were not considered to be treatment-related (one due to respiratory failure and one due to infection).

Comment: The bispecific T-cell engager agent blinatumomab has been a successful introduction into the treatment of patients with ALL who have relapse from previous therapy. This phase 2 study from the MD Anderson Cancer Centre addressed the potential role of this agent in front line therapy of Philadelphia-chromosome-negative patients with B-ALL in combination with hyper-CVAD. Blinatumomab was added after 4 cycles of chemo for 4 consolidation courses, before maintenance therapy with POMP alternating with blinatumomab. Thirty-eight patients with a median age of 37 years were enrolled in the study and there was a median follow up of 3 years where the relapse-free survival was 73%. There was a single patient who stopped therapy because of neurotoxicity. This sets the scene for randomised studies.

Reference: Lancet Haematol. 2022;9(12):e878-85
Abstract

Second primary malignancies in patients with haematological cancers treated with lenalidomide

Authors: Saleem K et al.

Summary: This was a systematic review and meta-analysis of RCTs that explored the risk of developing second primary malignancies with the use of lenalidomide across all haematological cancer settings. Researchers analysed data from 38 eligible trials comprising 14,058 patients, including 18 trials in multiple myeloma. Across all malignancies, there was an RR of 1.16 (95% CI 0.96—1.39), with heterogeneity across indications (p=0.020). When lenalidomide was administered in multiple myeloma settings, the RR rose to 1.42 (95% CI 1.09—1.84) with increased frequencies in both haematological and solid secondary primary malignancies in post- and no-transplantation. However, there was no increased risk of secondary primary malignancies for myelodysplastic syndrome (RR 0.96; 0.23—3.97) or lymphoma or CLL (RR 0.90; 0.76—1.08).

Comment: Lenalidomide has been the most successful introduction for a new myeloma active drug this century. A small hiccup in the growth of its use occurred with the observation of an apparent increase in the rate of second malignancies in patients taking the IMiD. Subsequent studies did not show this apparent toxicity. This review was designed to identify the risk of second primary malignancies in all uses of lenalidomide. Only studies with a follow up of 12 months or longer were included. Thirty-eight trials including ≈14,000 patients were eligible, and 18 of these studies were in multiple myeloma. Of interest was the fact that a signal for increased malignancies was only seen in the myeloma studies (relative risk of 1.42) but not in those of lymphoma, CLL or myelodysplasia.

Reference: Lancet Haematol. 2022;9(12):e906-18
Abstract

A phase 1 dose escalation study of the pyruvate kinase activator mitapivat (AG-348) in sickle cell disease

Authors: Xu JZ et al.

Summary: The safety and tolerability of multiple ascending doses of mitapivat in patients with sickle cell anaemia was assessed in this phase 1 study. Eligible patients (n=16) were treated with 5, 20 and 50mg ascending dose levels of mitapivat twice daily for 2 weeks each, and for nine patients this was increased to 100mg twice daily following a protocol amendment. The authors note that mitapivat was a viable therapeutic approach which was tolerated well at all dose levels. Insomnia, headache and hypertension were the most common treatment-emergent AEs. Overall, there were six serious AEs, including a pre-existing pulmonary embolism, four vaso-occlusive crises (VOCs) and non-VOC-related shoulder pain. No serious AEs were drug-related, except for possibly two VOCs which occurred during drug taper. At the dose of 50mg twice daily the mean haemoglobin increase was 1.2g/dL and a ≥1 g/dL increase in haemoglobin response from baseline was achieved by 56.3% of patients. Patients also experienced dose-dependent reductions in 2,3-diphosphoglycerate concentration, increases in adenosine triphosphate levels, and mean reductions in haemolytic markers.

Comment: We continue to monitor reports of potential treatments for patients with sickle cell disease, a significant worldwide problem that appears to be a rare disease in Australia, but which utilises proportionately more health care resources than its prevalence would suggest. This phase 1 study of mitapivat, a pyruvate kinase activator, was completed in 16 patients with sickle cell disease. It was tolerated well at all dose levels and biological activity, identified by apparent reduced VOCs with some event occurring during drug dose taper. Clinically significant haemoglobin increases were seen at the highest dose level used (50mg twice daily). This is a promising agent deserving of further study.

Reference: Blood. 2022;140(19):2053-62
Abstract

Incidence and impact of anticoagulation-associated abnormal menstrual bleeding in women after venous thromboembolism

Authors: De Jong CMM et al.

Summary: The incidence of abnormal uterine bleeding in women treated with anticoagulants for acute venous thromboembolism (n=98; aged 18-50 years) was examined in this international multicentre prospective cohort study. Baseline menstrual blood loss was assessed for the last menstrual cycle before the diagnosis of venous thromboembolism, and then measured prospectively during 3-6 months of follow-up for each cycle through the use of a pictorial blood loss assessment chart of self-reported abnormal uterine bleeding. QoL scores were recorded using the Menstrual Bleeding Questionnaire. At follow-up, two out of every three women (66%) had experienced abnormal uterine bleeding (95% CI 57.0—75.0), 60% of whom did not experience abnormal uterine bleeding before a venous thromboembolism diagnosis (95% CI 47.0—71.0). QoL decreases over time were only observed in women with new-onset abnormal uterine bleeding, with a mean score increase of 5.1 points (95% CI 2.2—7.9). The researchers noted that due to the COVID-19 pandemic recruitment was slow, and the study was terminated early.

Comment: The use of modern anticoagulation has increased safety and outcomes in patients after venous thromboembolism. This study from The Netherlands specifically examined the rate of abnormal menstrual bleeding in women aged 18-50 years on anticoagulants in this setting. A pictorial menstrual blood loss score was used, and an associated QoL questionnaire was implemented to correlate clinical effects. The COVID-19 pandemic limited accrual but 98 women were entered into the study, and 65 met a definition of abnormal uterine bleeding - more than half of whom had not had this prior to commencing anticoagulants. QoL decreased but only in women with new-onset abnormal uterine bleeding. This suggests that more attention needs to be given to this patient group and mitigation strategies studied.

Reference: Blood. 2022;140(16):1764-73
Abstract

Efficacy and safety of avapritinib in previously treated patients with advanced systemic mastocytosis

Authors: Reiter A et al.

Summary: The safety and efficacy of avapritinib, a potent highly selective *KIT* D816V-mutant inhibitor, was evaluated in these pooled analyses of evaluable patients with advanced systemic mastocytosis who had received ≥1 systemic therapy prior to avapritinib in the EXPLORER and PATHFINDER clinical studies (n=31). There was an overall response rate of 71% (95% CI 52.0—86.0; median time to response 2.3 months), with 19% of patients achieving complete remission with partial recovery of peripheral blood counts (median time to remission 7.4 months). The majority of patients achieved reductions ≥35% in spleen size (70%) and decreases ≥50% in serum tryptase (89%), bone marrow mast cell infiltration (89%) and *KIT* D816V variant allele fraction (66%). Avapritinib showed efficacy across all subtypes of advanced systemic mastocytosis, regardless of poor prognostic somatic mutations or type/number of prior therapies. Neither duration of response nor overall survival were reached. A total of 94% of patients experienced treatment-related AEs, most of which were grade 1/2. Grade 3 AEs occurred in 57% of patients, and at 6 months 81% continued treatment.

Comment: Systemic mastocytosis makes an appearance in these pages frequently, indicating the need for new effective therapies particularly in the advanced form of the disease. This was an analysis of multiple studies of a potent inhibitor of the *KIT* mutation, avapritinib, in patients who had had at least one prior systemic therapy. There were 31 evaluable patients with a response rate of 71% including 19% with complete remission which took a median of 7 months to occur. Median duration of response was not reached. This high response rate in patients who had failed prior therapy is encouraging.

Reference: Blood Adv. 2022;6(21):5750-62
Abstract

Patient- and physician-reported pain after tyrosine kinase inhibitor discontinuation among patients with chronic myeloid leukemia

Authors: Flynn KE et al.

Summary: This was a prospective, single-arm, longitudinal clinical trial conducted across 14 US sites which assessed patient- and physician-reported pain in evaluable patients with optimally treated chronic myeloid leukaemia (n=172) after discontinuing TKI therapy. Prior to enrolment in the study, the median duration of TKI therapy was ≈7 years. Following TKI discontinuation, physician-reported pain-related AEs were recorded in 20.4% of patients in the first 3 months (15.1% at 1 month; 6.4% at 2 months; 2.9% at 3 months; 5.8% >3 months), and the maximum pain grade was rated as 'mild' for the majority of these patients. A ≥1 category increase in musculoskeletal pain was reported by 62% of patients between baseline and 3 months after TKI discontinuation, while a ≥2 category increase was reported by 13%. A total of 154 patients reported changes in medications at 3 months, 18 (11.7%) of whom started taking an additional medication for pain (11 prescription medication; 8 over-the-counter medication; 1 both), and three patients (1.7%) recommenced a TKI due to pain. For patients who both did and did not restart TKI, trajectory modelling revealed that pain increased in the first 3 months before decreasing to baseline by 6 months, followed by additional decreases.

Comment: Imatinib was a truly revolutionary therapy when introduced into the management of chronic myeloid leukaemia over 29 years ago. This agent and the multiple next generation TKIs truly altered the face of this previously rapidly fatal disease. In recent years, the observation that some patients can stop therapy and maintain a treatment-free remission has suggested that these therapies can, in some patients, produce a functional cure. In trials of such withdrawal of therapy, musculoskeletal pain has been reported with variable frequency and this study from the USA is the first attempt to document patient-reported pain in this setting. It was a 14-centre study in which 172 patients were studied. Within 3 months of discontinuation, 20% had physician-reported pain and 13% had an increase in self-reported pain, while 12% of patients started analgesia. Interestingly, three patients recommenced their TKI because of pain. Modelling predicted an increase in pain in the first 3 months with a decrease to baseline by 6 months.

Reference: Haematologica. 2022;107(11):2641-9
Abstract

Expert commentary by Professor Jeff Szer AM.

Professor Jeff Szer AM (@marrow) is a member of the Clinical Haematology team at Peter MacCallum Cancer Centre and The Royal Melbourne Hospital. He is also immediate past President of the World Marrow Donor Association and a past President of the Worldwide Network for Blood and Marrow Transplantation. He established the first adult bone marrow transplant centre in Melbourne in 1984. His clinical research interests are in all aspects of haematology, focussing on improving the outcomes of treatment for leukaemia, lymphoma and myeloma, and in several classical haematological conditions. He has published over 380 peer-reviewed papers and is the Editor-in-Chief of the Internal Medicine Journal, and is on the editorial boards of several other international journals.

A real-word experience of eltrombopag plus rabbit antithymocyte immunoglobulin–based IST in Chinese patients with severe aplastic anemia

Authors: Jin Y et al.

Summary: The real-life impacts of low doses of eltrombopag, a thrombopoietin receptor agonist, combined with ATG-based immunosuppressive therapy in treatment-naïve Chinese patients with severe aplastic anaemia were explored in this multicentre registry of the Chinese Eastern Collaboration Group of Anaemia. Eligible patients were administered either immunosuppressive therapy with additional eltrombopag (combination therapy; n=54) or immunosuppressive therapy alone (n=67). Patients in the combination arm had significantly higher overall response rates than those receiving immunosuppressive therapy alone at 1 (p=0.002), 3 (p=0.028), 6 (p=0.006) and 12 months (p=0.031), however no significant differences were observed in the complete response rates between the two treatment arms. Patients in the combination group had improved 2-year overall survival compared to those in the immunosuppressive group (98% vs. 88%, respectively; p=0.078), and both cohorts experienced similar rates of AEs.

Comment: Eltrombopag has been shown in elegant studies in the US to improve bone marrow function in patients with bone marrow failure and in combination with ATG, improve outcomes of patients with severe aplastic anaemia. This was a real-world experience in China of patients treated with ATG plus eltrombopag for severe aplastic anaemia. One hundred and twenty-one patients were enrolled in a registry and followed closely; 54 received combination therapy and 67 immunosuppressive therapy alone. The combination group had a higher overall response rate at 1, 3, 6 and 12 months, and the 2-year overall survival rates were 98% and 88%, respectively. AEs were similar in the two groups.

Reference: Ann Hematol. 2022;101(11):2413-9
Abstract

Efficacy and steroid-sparing effect of tacrolimus in patients with autoimmune cytopenia

Authors: Zhang R et al.

Summary: The safety, efficacy and steroid-sparing impacts of tacrolimus in patients with autoimmune cytopenia (immune thrombocytopenia, autoimmune haemolytic anaemia and Evan syndrome) were assessed in this clinical study. Eligible patients (n=318; 27.4% male; median age 45 years) were administered either tacrolimus with steroids (tacrolimus group; n=144), or steroids alone (control group; n=174). Both groups had comparable overall response rates and total side effects, however compared to those in the control group, patients who received tacrolimus had a higher optimal complete response rate (p<0.05), reduced relapse rate, prolonged relapse-free survival (p<0.05), lower cumulative steroid dosage, earlier discontinuation of steroids (p<0.05) and reduced incidence of steroid-related AEs (p<0.05).

Comment: Immune thrombocytopenia, autoimmune haemolytic anaemia and Evan syndrome are all treated with immune suppression based on corticosteroids. This study looked at the addition of the calcineurin inhibitor tacrolimus to steroids in a randomised study of such patients. A total of 318 patients were enrolled, with the majority having immune thrombocytopenia. Overall, response rates were similar, however the tacrolimus group had a decreased relapse rate, prolonged relapse-free survival and importantly, lower cumulative steroid dosing with earlier discontinuation of steroids. This looks like a promising addition to the treatment of autoimmune cytopenic syndromes.

Reference: Ann Hematol. 2022;101(11):2421-31
Abstract

JAK inhibition with ruxolitinib in relapsed or refractory classical Hodgkin lymphoma

Authors: Gillessen S et al.

Summary: This paper reported on the final results of the phase 2, open label, multicentre clinical trial, JeRiCHO, which explored the clinical outcomes of administering ruxolitinib, a JAK inhibitor, to patients with relapsed or refractory classical Hodgkin lymphoma. Evaluable patients (n=12; age range 17-76 years; 12 male; 2 female) who failed second-line treatment were administered oral ruxolitinib 25mg twice daily in 28-day cycles until disease progression or intolerable toxicity. In stage 1 after 2 treatment cycles, six patients had progressive disease, three had a stable disease and two had a partial response. The 1-year median overall survival was not met, and the median PFS was 3.6 months. One grade 4 AE affecting the respiratory tract was reported. Due to a premature termination of the trial, no patients were enrolled in stage 2. All 12 patients discontinued treatment, with eleven patients ceasing following disease progression, two due to violation of inclusion and exclusion criteria and one owing to pneumonia interrupting treatment for >8 weeks. Six patients died during the study duration, with almost all cases related to Hodgkin lymphoma.

Comment: In an unusual setting, the JAK inhibitor ruxolitinib, most usually applied in myeloproliferative neoplasms, was studied in classical Hodgkin lymphoma patients relapsing after second-line therapy. This phase 2 study from Germany was based on promising preclinical data and the known low toxicity rate of the agent. This was a small study of 12 adult patients treated with ruxolitinib at a dose of 25mg twice daily. Two had a partial response and three had stable disease, while six had progressive disease. A median PFS of 3.6 months suggested only a modest degree of efficacy, although toxicity was very mild. The study did not continue.

Reference: Eur J Haematol. 2022;109(6):728-35
Abstract

Australian Research Review subscribers can claim CPD/CME points for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our CPD page.

Research Reviews are prepared with an independent commentary from relevant specialists. To become a reviewer please email geoff@researchreview.com.au.

Research Review Australia Pty Ltd is an independent Australian publisher. Research Review receives funding from a variety of sources including Government depts., health product companies, insurers and other organisations with an interest in health. Journal content is created independently of sponsor companies with assistance from leading local specialists. **Privacy Policy:** Research Review will record your email details on a secure database and will not release them to anyone without your prior approval. Research Review and you have the right to inspect, update or delete your details at any time. **Disclaimer:** This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.

Research Review publications are intended for Australian health professionals.

RESEARCH REVIEW™ Australia's Leader in Specialist Publications

