Lymphoma & Leukaemia Research Review™

Making Education Easy

Issue 92 - 2025

In this issue:

Abbreviations used in this issue:

PCNSL = primary central nervous system lymphoma;
MMR = major molecular response.

Earn CPD

Royal Australasian College of Physicians (RACP) MyCPD participants can claim the time spent reading and evaluating research reviews as CPD in the online MyCPD program. Please contact MyCPD@racp.edu.au for any assistance.

Royal Australian & New Zealand College of Radiologists (RANZCR) members can claim reading related to their practice as a CPD activity under the category 'journal reading and web based no certificate *reflection required'. More info.

RESEARCH REVIEW™
Australia's Leader in Specialist Publications

Welcome to issue 92 of Lymphoma & Leukaemia Research Review.

This review begins with a randomised, phase II trial, where seven-year follow-up data from the AATT study was analysed to determine the consolidation of autologous and allogeneic transplantation. Another interesting study included is a multicentre, phase II trial, which examined the efficacy of venetoclax plus decitabine as a first-line therapy for elderly acute myeloid leukaemia patients. This review concludes with a real-world data study, which aimed to determine if R-CHOEP is superior to R-CHOP for diffuse large B-cell lymphoma.

We hope you enjoy this update in lymphoma and leukaemia research, and we look forward to receiving comments and feedback.

Kind Regards,

Dr Pietro Di Ciaccio
pietro.diciaccio@researchreview.com.au

Long-term follow-up of the prospective randomized AATT study (autologous or allogeneic transplantation in patients with peripheral T-cell lymphoma)

Authors: Tournilhac O et al.

Summary: In this randomised, phase II trial, researchers examined the 7-year follow-up of the AATT study, where the consolidation of alloHCT and autoHCT was explored. Patients included had stage II to IV T-cell lymphoma and were aged 18 to 60 years. Each patient was randomly allocated to receive either alloHCT (n=26) or autoHCT (n=41). The analysis revealed that patients in the alloHCT group achieved a 7-year event-free survival of 38% (95% CI 25 to 52), compared to 34% (22 to 47) for those receiving autoHCT. Additionally, patients in the alloHCT group had an OS of 55% (41 to 69), while those receiving autoHCT had an OS of 61% (47 to 74). The cumulative progression/relapse rate was 8% (0 to 19) in the alloHCT group, compared to 55% (35 to 74) in the autoHCT group, with non-relapse mortality rates of 31% (13 to 49) and 3% (0 to 8), respectively. These findings do not support the use of alloHCT as first-line consolidation.

Comment: The optimal approach to consolidation of patients with peripheral T cell lymphoma, following first-line chemotherapy, is controversial. This study from French and German groups, randomised young, fit patients to consolidation with either allogeneic or autologous haematopoietic cell transplant. This is an important study, given there are relatively good data of an active graft-versus lymphoma effect in T cell lymphoma. OS in both arms was similar, with a dramatic reduction in relapse rates for alloHCT, offset by increased non-relapse mortality. The critical result from longer term follow-up, is patients salvaged after relapse following autoHCT, who went on to receive alloHCT, had a long-term OS of 61% (numerically superior to those who had frontline alloHCT). Consequently, alloHCT cannot be recommended as standard first line consolidation in PTC. Importantly, half of the participants relapsing after autoHCT did not go on to alloHCT, and the management of these patients remains a substantial challenge.

Reference: J Clin Oncol. 2024;10;42(32):3788-3794.
Abstract

Safety and efficacy of odronextamab in patients with relapsed or refractory follicular lymphoma

Authors: Kim TM et al.

Summary: Within this phase II study, the efficacy of odronextamab was evaluated. Those included (n=128) had R/R FL and had previously received at least two or more lines of systemic therapy. Each patient received the study treatment in 21-day cycles, with step-up dosing in cycle 1 to decrease the risk of cytokine release syndrome. Post-analysis, the majority of patients (95%) completed cycle 1, and 85% of patients completed four or more cycles. After 20.1 months of follow-up, patients achieved an ORR of 80.0% and a CR rate of 73.4%. The median CR and PFS were 25.1 months and 20.7 months, respectively, though the median OS was not reached. Cytokine release syndrome, neutropenia, and pyrexia were the most common treatment-related AEs. Odronextamab demonstrated a generally manageable safety for this patient population.

Comment: R/R FL currently lacks a standard of care in management, and can be a challenging entity to treat, in particular in the context of early progression (POD24). CD20xCD3 bispecific agents represent an addition to the armoury in this setting. This phase II study of the bispecific agent odronextamab reflects the high activity of this agent in R/R FL, with OR and CR rates of 80% and 73% respectively, similar to other bispecific agents in this space. Virtually all CRs were obtained prior to cycle 3 (28 day cycles), with the failure to achieve a CR a strong predictor of OS (median OS not reached for CRs versus 18 months for PRs). Importantly, the majority of patients suffered an infective complication at some stage, approximately one-third COVID-19. The administration was also somewhat cumbersome, with IV administration and compulsory hospitalisation for multiple level step-up doses throughout the first cycle. This is an unattractive feature compared with competing agents, and of note far less stringent inpatient requirements have been mandated for the ongoing phase III trial.

Reference: Ann Oncol. 2024;35(11):1039-1047.
Abstract

Late subsequent leukemia after childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS)

Authors: Ghosh T et al.

Summary: The risk factors, prevalence, and outcomes for late and very late leukaemia among survivors of childhood cancer were evaluated in this study. A total of 25,656 five-year survivors were included for analysis. The results showed that 77 patients developed subsequent leukaemia, 49 of whom had late leukaemia (median time for diagnosis 7.8 years) and 28 with very late leukaemia (25.4 years), resulting in a cumulative incidence rate of 0.23% (95% CI 0.18 to 0.30). AML, myelodysplastic syndrome, and chronic myeloid leukaemia were the most commonly reported leukaemia subtypes. Additionally, when compared to the general population, survivors had an increased risk of developing both late leukaemia (SIR 9.3, 7.0 to 12.1) and very late leukaemia (5.9, 3.9 to 8.4). In summary, these results indicate that survivors are at a greater risk of developing subsequent leukaemia.

Comment: Subsequent myeloid malignancies, predominantly MDS and AML, are well-described complications of patients receiving cytotoxic chemotherapy, in particular alkylators and topoisomerase inhibitors, as well as radiotherapy. The latency is usually relatively short (2-7 years); however, the onset may be delayed many years after this, an issue of particular relevance to paediatric and young adult survivors. It is also worth noting, that although prospective trials may report second cancer incidence, follow up uncommonly exceeds 10 years in such trials. This interesting retrospective cohort study from the US and Canada included 25,565 survivors diagnosed with their initial cancers under 21 years of age. Important findings were a nine-fold increase in risk of late leukaemia compared with the general population, with incidence highest in survivors of ALL and NHL. There was a persistent incidence over time without plateau, which has implications for long term follow up of high-risk patients. Important risk factors included cumulative etoposide/tenoposide exposure, haematopoietic cell transplant and smoking.

Reference: Cancer Med. 2024;13(20):e70086.
Abstract

Venetoclax plus decitabine as a bridge to allogeneic haematopoietic stem-cell transplantation in older patients with acute myeloid leukaemia (VEN-DEC GITMO): final report of a multicentre, single-arm, phase 2 trial

Authors: Russo D et al.

Summary: This multicentre, single-arm, phase 2 trial conducted in 20 centres across Italy examined the efficacy of venetoclax plus decitabine as a first-line therapy. Those included were aged ≥60 and <75 years and had newly diagnosed AML. Ninety-three patients (median age 68.5 years, 100% White, 54% male) were enrolled between June 1, 2021, and December 30, 2022, all of whom received the study treatment. After a median follow-up of 236 days, the majority of patients (69%) reached CR, with 57% undergoing allogeneic HSCT in CR. Out of 64 patients who were in CR, five (8%) relapsed prior to transplantation, and four died as a result. The majority of patients (53%) experienced a grade 3 or higher AE, with the most common being infections (57%), neutropenia (35%), thrombocytopenia (4%), and cardiac events (8%). No treatment-related deaths were reported. Overall, the results from this study suggest that venetoclax plus decitabine may enhance the feasibility of allogeneic HSCT for this patient population.

Comment: The optimal management of older, but not frail, patients with AML often presents a challenge, often flirting with the threshold of allogeneic HCT transplant eligibility. Transplant in intermediate and high-risk AML is usually the ideal consolidation strategy; however, often older transplant-eligible patients may experience toxicity with standard induction and consolidation regimens which make subsequent transplantation difficult. Evidence of a less intensive venetoclax/hypomethylating agent induction strategy to "get" these patients to transplant is emerging and is an increasingly adopted practice in some centres. For patients with low-risk AML, who may be cured with high dose induction and consolidation without transplant, should ideally be treated with this strategy wherever possible, however.

Reference: Lancet Haematol. 2024;11(11):e830-e838.
Abstract

Lymphoma & Leukaemia Research Review™

Independent commentary by Dr Pietro Di Ciaccio

Pietro Di Ciaccio is a staff specialist haematologist at The Canberra Hospital, and laboratory haematologist at Capital Pathology. He has particular clinical and research interests in lymphomas, and haematological cancers in pregnant women.

Earn CPD

CPD Home. Subscribers can claim the time spent reading and evaluating research reviews as an Educational Activity: Professional Reading in the CPD Tracker. Please Contact Us for support.

Asciminib monotherapy as frontline treatment of chronic-phase chronic myeloid leukemia: results from the ASCEND study

Authors: Yeung DT et al.

Summary: In this study, researchers evaluated the efficacy of asciminib for newly diagnosed chronic-phase chronic myeloid leukaemia. Each patient received 40mg of asciminib twice daily. After a median follow-up of 21 months, it was found that AEs (6%), loss of response (4%), and withdrawn consent (5%) were the most common reasons for treatment discontinuation. No deaths were reported, though one patient developed lymphoid blast crisis. Ninety-three percent of patients achieved early molecular response (96% CI 86 to 97), and 79% achieved major molecular response by 12 months (95% CI 70 to 87). These results suggest that asciminib demonstrated excellent tolerability and may lead to high rates of molecular response.

Comment: Asciminib is a novel TKI, with a mechanism diverse to that of more traditional ATP-binding site TKIs (imatinib, nilotinib, dasatinib). Its activity in CML patient's refractory to at least two prior TKIs has been established in the ASCEMBL trial (Rea et al, Blood 2021) and it is now reimbursed in Australia for this indication. The Phase 2 ASCEND study from the ALLG group explored the use of asciminib in the frontline treatment of chronic-phase CML. The coprimary endpoint was MMR (BCR::ABL <0.1%) at 12 months, achieved in 93% of patients. These results must be interpreted in the context of the subsequently published ASC4FIRST trial (Hocchaus et al, NEJM 2024), which randomised treatment-naïve chronic phase CML patients to either asciminib or an investigator's choice of imatinib or a second-generation tyrosine kinase inhibitor. Although the study met its primary outcome of higher major molecular response (MMR) rates in the experimental group (67.7% versus 49%), the comparison to both 1st gen (imatinib) and 2nd gen (nilotinib, dasatinib) TKIs was not ideal. The superior MMR rate of asciminib over imatinib in ASC4FIRST is hardly surprising, but crucially no difference in terms of MMR rates was found between asciminib and 2nd-gen TKIs in this study. Grade ≥3 elevation in pancreatic enzymes is an AE to be aware of, noted in both trials at a rate of 2-3%.

Reference: Blood. 2024;7;144(19):1993-2001.
Abstract

Outcomes with single-agent gilteritinib for relapsed or refractory FLT3-mutant AML after contemporary induction therapy

Authors: Othman J et al.

Summary: This study described the outcomes of gilteritinib among patients with R/R FLT3-mutant AML who had previously received contemporary induction therapy. A large, real-world cohort of 152 patients (median age 61 years) was utilised, based in 38 UK hospitals. A significant proportion of patients (36%) had received 2 or more prior lines of therapy, with 41% having received a FLT3 inhibitor and 24% having received venetoclax. After a median of 4 cycles of gilteritinib, over half (56%) of the patients required hospitalisation during the first cycle, and the majority also required a transfusion in each of the first 4 cycles. Twenty-one percent of patients achieved CR, while 9% had a CR with incomplete recovery. Furthermore, those with FLT3-tyrosine kinase domain mutations or adverse karyotypes had lower remission rates. A multivariable analysis also revealed that increasing age, KMT2A rearrangement, and complex karyotype were all associated with worse survival. Overall, these findings suggest that gilteritinib may lead to suboptimal results.

Comment: The phase 3 ADMIRAL study (Perl et al, NEJM 2019) established the activity of the FLT3 inhibitor gilteritinib in R/R FLT3-TKD and -ITD mutant AML, with superior OS compared with salvage chemotherapy. Inclusion in this trial, was, however limited to one prior line of therapy, no patients had received prior venetoclax and only a small number prior FLT3 inhibition. Of course, the treatment landscape of AML has evolved, with venetoclax/azacitidine for older/frailer patients, as well as upfront midostaurin with chemotherapy for fit, FLT3-mutated patients. This valuable series, authored by an expatriated Australian haematologist, describes contemporary, real-world data of gilteritinib outcomes. Median OS of 9.5 months was very similar to that of ADMIRAL, despite 41% receiving prior FLT3 inhibitors, 36% ≥2 prior lines of therapy and 24% venetoclax. Survival is still suboptimal, however there were some longer-term survivors bridged to allogeneic HCT.

Reference: Blood Adv. 2024;12;8(21):5590-5597.
Abstract

Ibrutinib plus rituximab and mini-CHOP in older patients with newly diagnosed DLBCL: a phase 2 ALLG study

Authors: Verner E et al.

Summary: The addition of ibrutinib to RminiCHOP was evaluated in this multicentre, prospective phase 2 trial. Patients included had newly diagnosed DLBCL and were 75 years or older, all of whom received six 21-day cycles of the study treatment followed by two 21-day cycles of R-ibrutinib. After a median follow-up of 35.5 months, patients achieved a 2-year OS of 68% (95% CI 55.6 to 77.4) and a PFS of 60.0% (47.7 to 70.3). Additionally, patients achieved an ORR of 76% (61/79) and a CR rate of 71% (56/79). There were 34 deaths reported (43%), and the majority of those included (67%) experienced at least one serious AE. These results suggest that ibrutinib in RminiCHOP may offer efficacious outcomes for elderly DLBCL patients.

Comment: There have been numerous attempts over the last two decades to improve upon the R-(mini)CHOP backbone in DLBCL with the addition of novel agents, with thus-far limited success. The PHOENIX trial of RCHOP +/- ibrutinib in DLCBL revealed substantial challenges in delivering this combination to patients over 60 due to toxicity. In an effort to improve deliverability, this phase II single-arm study reverted to a RminiCHOP backbone, with compulsory growth factor support. The authors should be congratulated for selecting OS and not PFS as the primary endpoint of the study. Unfortunately, the 2-year OS of 68% was not significantly superior to historical RminiCHOP data (Peyrade et al, Lancet Oncol 2011), even though this trial accepted patients as young as 75, whereas the reference study only went down to 80. Cell of origin did not affect outcomes, though numbers were small. Of note, over a quarter of patients in this study had grade 3 or greater infections, and half reported diarrhoea as an AE. Further study of ibrutinib in DLBCL is not currently planned, and its use based on this study is unfortunately difficult to broadly recommend.

Reference: Blood Adv. 2024;12;8(21):5674-5682.
Abstract

Efficacy and safety of gilteritinib versus sorafenib as post-transplant maintenance in patients with FLT3-ITD acute myeloid leukemia

Authors: Yeh J et al.

Summary: Within this retrospective analysis, researchers compared the safety and efficacy of gilteritinib to sorafenib as a post-transplant maintenance treatment. Patients included had FLT3-ITD AML and had previously received alloHCT between June 1, 2016, and December 31, 2020. A total of 55 patients were included, with 27 receiving gilteritinib and 29 receiving sorafenib. After analysis, those receiving gilteritinib remained on treatment for a median of 385 days, compared to 315 days for sorafenib. Both treatments showed similar 1-year PFS and relapse incidences; gilteritinib with 66% versus 76% for sorafenib (p=0.4), and 19% versus 24% (p=0.6) for relapse incidence, respectively. Both groups also experienced a high incidence of grade 3-4 haematological toxicity, particularly neutropenia (gilteritinib: 45%, sorafenib: 34%) and thrombocytopenia (gilteritinib: 30%, sorafenib: 52%). Additionally, 44% of patients receiving gilteritinib and 14% of patients receiving sorafenib did not discontinue maintenance. In summary, these results suggest that sorafenib and gilteritinib have comparable toxicity profiles.

Comment: FLT3-ITD mutated AML, without high-risk karyotype, has been classified as intermediate-risk by the latest iteration of the European Leukaemia Network AML guidelines, published in 2022. It is generally accepted, that in eligible patients, consolidation with alloHCT is the optimal strategy. Given the largely bleak outcomes of relapsed FLT3-mutated AML, there is great interest in optimal maintenance strategies post alloHCT. The use of the first-generation FLT3 kinase inhibitor sorafenib was investigated in the phase 2 randomised SORMAIN trial, where 24 months of sorafenib maintenance was associated with reduced rates of death and relapse (Burchert et al, J Clin Oncol 2020). Similarly, the larger phase 3 MORPHO study investigated the implementation of post-transplant maintenance with the second-generation FLT3-inhibitor gilteritinib. This study did not show a reduction in relapse overall, though a post hoc analysis suggested a benefit in post-transplant MRD-positive patients. A similar suggestion was noted in the SORMAIN data. Neither agent is reimbursed in Australia in the post-transplant maintenance setting.

Reference: Clin Lymphoma Myeloma Leuk. 2024;24(11):e819-e826.
Abstract

Combination of rituximab and methotrexate followed by rituximab and cytarabine in elderly patients with primary central nervous system lymphoma

Authors: Yi JH et al.

Summary: In this phase 2 study, the efficacy and safety of rituximab plus high-dose methotrexate was evaluated. Patients included had newly diagnosed primary central nervous system lymphoma (PCNSL) and were 60 years or older, all of whom received high-dose methotrexate plus rituximab, followed by two cycles of cytarabine plus rituximab as consolidation treatment. A total of 35 patients were included, with a median age of 73 years. Post-analysis revealed that patients achieved a CR of 56% and a partial response of 20%, respectively. Twenty-six patients continued to receive the consolidation treatment, reaching a CR of 59% and a partial response of 9%, respectively. Following a median follow-up of 36.0 months, patients had a 2-year PFS of 58.7%. Three patients were removed from the study due to toxicities, although no treatment-related mortalities were reported. Overall, these results suggest that the study treatment may be a feasible option for this patient population.

Comment: Whilst for younger, fit patients with PCNSL, the emerging standard of care is intensive high-dose methotrexate-based induction, with thiotepa-based autologous HCT consolidation, these regimens are often too toxic for older patients. The optimal approach to care in that setting is far less clear. This interesting study from Korea investigated a sequential approach of five to seven cycles of R-high dose methotrexate, "consolidated" with two cycles of R-cytarabine in responding patients. Thirty-five patients were included, with a median age of 73. Only 37% had an ECOG of 0-1. Crucially, dose reduction of methotrexate was required only in 9% of patients, a lower number than in some other trials in this space. The delivery of HDMTX at target doses positively impacts survival in older PCNSL patients (Martinez-Calle et al, BJH 2020). Two-year PFS and OS rates of 59% and 89% compare somewhat favourably to those of the larger PRIMAIN study (Fritsch et al, Leukemia 2017), a regimen incorporating HDMTX with induction and maintenance procarbazine in older patients with PCNSL.

Reference: Br J Haematol. 2024;205(5):1773-1781.
Abstract

Effectiveness of R-CHOP versus R-CHOEP for treatment of young patients with high-risk diffuse large B-cell lymphoma: A Danish observational population-based study

Authors: Jørgensen RRK et al.

Summary: This real-world data study examined the efficacy of R-CHOEP over R-CHOP. Those included derived from the Danish Lymphoma Register, all of whom were 18-60 years old and diagnosed with DLBCL between 2006 and 2020. A total of 396 patients were randomised (1:1) to receive either R-CHOEP (n=213) or R-CHOP (n=183). Post-analysis revealed that those in the R-CHOEP group achieved a 5-year unadjusted PFS of 69% (95% CI 63 to 76) and OS of 79% (73 to 85), compared to 62% (55 to 70) and 76% (69 to 82) in the R-CHOP group (log-rank test, PFS: p=0.25 and OS: p=0.31). Furthermore, after matching patients from the R-CHOP group to the R-CHOEP group, the 5-year PFS and OS for R-CHOEP were 65% (57 to 74) and 79% (72 to 84), versus 63% (55 to 73) and 79% (72 to 87) for those in the R-CHOP group (log-rank test, PFS: p=0.90 and OS: p=0.63). The superiority of R-CHOEP over R-CHOP was not confirmed by this study.

Comment: Beginning with the seminal Fisher study in 1993, efforts to improve on outcomes in DLCBL by intensifying the R-CHOP backbone have largely met with limited, if any, success. Evidence to support the addition of etoposide to R-CHOP has derived largely from three studies. First, the German DSHNHL 2002-1 study, where young patients with high-risk DLBCL treated with 8 cycles of RCHOEP14 had a comparatively excellent 3-year event-free survival of 74% (Schmitz et al, Lancet Oncol 2012). Further large retrospective studies from both Denmark (Gang et al, Ann Oncol 2012) and Sweden (Wasterlid et al, Haematol Oncol 2017), suggested a PFS and OS advantage of RCHOEP14 respectively. This study is a more contemporary analysis of that same Danish database, with longer follow up compared to the 2012 study, also with deployment of statistical matching techniques. Although there were certain imbalances still between groups, the conclusions are likely to dampen enthusiasm for RCHOEP, except for perhaps certain highest risk patients.

Reference: Eur J Haematol. 2024;113(5):641-650.
Abstract