Lymphoma & Leukaemia Research Review™

Making Education Easy

Issue 74 - 2023

In this issue:

Abbreviations used in this issue:

AE = adverse event; **(allo-) HSCT** = (allogeneic) hematopoietic stem cell transplant; **AML** = acute myeloid leukaemia; **CR** = complete response; **EFS** = event-free survival; **FIL** = Italian Lymphoma Foundation; **GVHD** = graft versus host disease **HR** = hazard ratio; **LBCL** = large B-cell lymphoma; **LYSA** = Lymphoma Study Association; **MDS** = myelodysplastic syndrome; **(MP-) CMML** = (myeloproliferative) chronic myelomonocytic leukaemia; **MRD** = measurable residual disease; **OS** = overall survival; **PET** = positron emission tomography; **PFS** = progression-free survival; **QOL** = quality of life; **RFS** = relapse-free survival; **R-MiniCHOP** = rituximab CYCLOPHOSPHamide DOXOrubicin vinCRISTine prednisolone; **(R/R) B-ALL** = (relapsed/refractory) acute lymphoblastic leukaemia; **(R/R) T-ALL/LBL** = relapsed/refractory T-cell acute lymphoblastic leukaemia & lymphoma; **TGA** = Therapeutic Goods Administration.

Claim CPD/CME points Click here for more info.

Welcome to issue 74 of Lymphoma & Leukaemia Research Review.

In this issue, we begin with a 3-year update of the ELIANA trial which shows that tisagenlecleucel provides durable survival and QOL improvements in paediatric and young adult patients with R/R B-ALL. This is followed by a global phase 3 study which supports the use of lisocabtagene maraleucel as a preferred second-line treatment versus standard of care in patients with primary refractory or early relapsed LBCL. Another paper of interest reports that patients aged >85 years with diffuse LBCL can benefit from a curative treatment approach with reduced-dose anthracycline and from rituximab within palliation. We conclude with a multi-centre study which suggests that allo-HSCT is a highly effective strategy in improving the long-term outcomes of patients with *TP53*-mutated AML.

We trust you find these studies and the others in this review interesting and informative for your clinical practice, and we look forward to reading your thoughts and feedback.

Kind Regards,

Associate Professor Stephen Larsen
stephen.larsen@researchreview.com.au

Three-year update of tisagenlecleucel in pediatric and young adult patients with relapsed/refractory acute lymphoblastic leukemia in the ELIANA trial

Authors: Laetsch TW et al.

Summary: Paediatric and young adult patients with relapsed or refractory acute lymphoblastic leukaemia (R/R B-ALL) administered tisagenlecleucel in the ELIANA trial experienced an overall remission rate of 81%, and at 12 months 59% remained relapse-free. In this updated analysis conducted at a median follow-up of 38.8 months, the overall remission rate was 82% and median EFS 24 months. At 3 years, EFS was 44% and OS was 63%, with the majority of events taking place during the initial 2 years following infusion; median OS was not reached. With censoring for subsequent therapy, estimated 3-year RFS was 52%, and without censoring this was 48%. Patient-reported QOL showed improvements at 36 months, and there were no novel AEs or safety concerns. The authors conclude that tisagenlecleucel is a curative treatment option for paediatric and young patients with R/R B-ALL.

Comment: The global phase 2 registration ELIANA trial led to the approval of tisagenlecleucel for the treatment of R/R B-ALL in paediatric and young adult patients (up to the age of 25), initially by the FDA in August 2017. In Australia it was approved by the TGA in January 2020 for this indication. This paper represents a 3-year update to provide long-term outcomes. With a total of 79 patients infused and a median follow-up of 38.8 months, the overall remission rate was 82%, with a median EFS of 24 months, and median OS was not reached. EFS was 44% and OS was 63% at 3 years overall. No new or unexpected long-term AEs were reported, and patients reported improvements in QOL up to 36 months after infusion. Of interest, B-cell aplasia persisted in 71% and 59% of patients at 12 and 24 months, respectively, with a median time to B-cell recovery (in responders) of 35.3 months. This update consolidates the curative potential of CAR T-cells, and the improvement in QOL over time emphasises the long-term tolerability of CAR T-cells.

Reference: J Clin Oncol. 2023;41(9):1664-9
Abstract

Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma

Authors: Abramson JS et al.

Summary: This was a primary analysis of the phase 3 TRANSFORM study, in which patients with primary refractory/early relapsed large B-cell lymphoma (LBCL) were randomised to either lisocabtagene maraleucel (n=92; 100 × 10^6 chimeric antigen receptor–positive T cells) or standard of care (n=92; 3 cycles platinum-based immunochemotherapy before high-dose chemotherapy + autologous stem cell transplantation in responders) as second-line treatment. At a median follow-up of 17.5 months, patients administered lisocabtagene maraleucel arm showed better EFS (not reached vs. 2.4 months), CR (74% vs. 43%; p<0.0001) and PFS (not reached vs. 6.2 months; HR 0.400; p<0.0001) than those who received standard of care.There was no statistically significant difference in OS between lisocabtagene maraleucel and standard of care (not reached vs. 29.9 months; HR 0.724; p=0.0987), however OS rates were 73% and 54%, respectively (HR 0.415), when adjusted for crossover from standard of care to lisocabtagene maraleucel. Among patients who received lisocabtagene maraleucel, grade 3 neurological events occurred in 4% and grade 3 cytokine release syndrome in 1%, with no grade 4/5 events.

Comment: This paper presents the primary analysis of the phase 3 TRANSFORM study, which compared lisocabtagene maraleucel with standard of care as second-line therapy for primary refractory or early relapsed LBCL. Standard of care was salvage chemotherapy followed by a BEAM autograft if they responded. The study found that treatment with lisocabtagene maraleucel resulted in significant improvements in EFS, CR, and PFS compared to standard of care. The median EFS was not reached for lisocabtagene maraleucel versus 2.4 months for standard of care, and the CR rate was 74% for lisocabtagene maraleucel versus 43% for standard of care. These data add to recent phase 3 studies of other CAR T-cell therapies in similar patient populations with second-line LBCL. ZUMA-7, with a median follow-up of 24.9 months, demonstrated that axicabtagene ciloleucel led to a significant improvement in the EFS (median EFS 8.3 vs. 2.0 months) and CR rate (65% vs. 32%) compared with standard of care. However, tisagenlecleucel was not shown to be superior to standard of care in the BELINDA study, with a median EFS of 3.0 months and a CR rate of 28% in both arms.

Reference: Blood. 2023;141(14):1675-84
Abstract

Brentuximab vedotin plus doxorubicin and dacarbazine in nonbulky limited-stage classical Hodgkin lymphoma

Authors: Abramson JS et al.

Summary: This phase 2 study investigated the safety and efficacy of brentuximab vedotin plus adriamycin (doxorubicin) and dacarbazine (BV-AD; 4-6 cycles based on interim PET response) without radiation in 34 patients with previously untreated nonbulky stage I-II Hodgkin lymphoma. The majority of patients received 4 cycles of therapy. There was an overall response rate of 100%, CR rate of 97%, and 2- and 5-year PFS of 95% and 91%, respectively. There were comparable rates of efficacy among patients with stage I and II disease and in patients with early favourable and unfavourable risk status. Grade 3 toxicities were experienced by 15% of patients, however no cases of grade ≥3 peripheral neuropathy occurred and there were no grade 4/5 AEs. Researchers noted that the toxicity profile of this treatment regimen was improved compared with brentuximab vedotin plus adriamycin, vinblastine and dacarbazinem (BV-AVD), and commented that further study into this regimen for Hodgkin lymphoma is warranted.

Comment: Whilst the historical standard of care treatment of early-stage favourable prognosis Hodgkin lymphoma is combined modality therapy with ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) followed by involved field radiotherapy, several chemotherapy-alone options have been explored. Compared with ABVD, BV-AVD has demonstrated encouraging efficacy both in advanced stage disease and in a phase 2 trial in nonbulky limited-stage disease, but at the cost of significantly increased peripheral neuropathy, neutropenia, and neutropenic fever. This study explores a regimen that also omits the vinblastine, BV-AD. Efficacy was encouraging with the overall and CR rates being 100% and 97%, respectively, with a 5-year PFS of 91%. The risks of neutropenia, neutropenic fever, and grade ≥2 peripheral neuropathy were markedly reduced compared with what has been observed in prospective trials of BV-AVD. Whilst promising, this study only has 34 patients and would need to be explored in larger randomised studies.

Reference: Blood Adv. 2023;7(7):1130-6
Abstract

Diffuse large B-cell lymphoma in octogenarians aged 85 and older can benefit from treatment with curative intent

Authors: Tucci A et al.

Summary: This report on patients enrolled in the Italian FIL Elderly Project compared the characteristics and outcomes of late octogenarians (n=129; >85 years) and early octogenarians (n=241; 80-85 years) with diffuse large B-cell lymphoma (LBCL) who were treated with either palliative or curative intent. Although the clinical characteristics were comparable between late and early octogenarians, a higher proportion of late octogenarians received palliative treatment (50% vs. 23%, respectively; p=0.001), with poorer 2-year OS (48% vs. 63%; p=0.001) and 2-year PFS (43% vs. 56%; p=0.01). Among patients treated with palliation, those who received rituximab had improved 2-year OS than those who did not (42% vs. 22%; p=0.008), and patients who received anthracycline experienced improved outcomes, with no difference between reduced or full doses. Risk categories were better identified by the Elderly Prognostic Index (EPI) than the simplified geriatric assessment, with high-risk EPI predicting poorer OS and PFS.

Comment: The management of diffuse LBCL patients older than 80 is becoming an increasingly relevant problem in clinical practice. However, most studies have an underrepresentation of patients older than 85 years of age. This study reported on a subset of the Elderly Project by the Italian Lymphoma Foundation (FIL), which is a large prospective study on 1163 older patients with diffuse LBCL older than 64. For patients older than 85, the 2-year OS was 48%, and there was a significantly better prognosis for those patients treated with curative intent with anthracycline-containing regimens (64%) than that of those receiving other regimens with palliative purpose (27%). The dose of anthracycline did not affect outcome which supports using a reduced dose of anthracycline in these patients; this confirms the results reported by the LYSA group using a R-MiniCHOP regimen. A further important observation was that the inclusion of rituximab in palliative regimens, or its use as a single agent, significantly improved survival compared with rituximab-free palliative regimens, regardless of age and patient fitness.

Reference: Haematologica. 2023;108(4):1083-91
Abstract

Survival of patients with mantle cell lymphoma in the rituximab era

Authors: Harmanen M et al.

Summary: The real-world survival of 564 patients with mantle cell lymphoma was examined in this retrospective binational analysis carried out between 2000-20. Overall, OS among this population was 77%, with a median OS of 80 months following diagnosis, and 5- and 10-year OS rates were 58% and 32%, respectively. Early disease progression was found to be a strong indicator of poor outcomes; patients who relapsed ≤24 months after finishing first-line treatment had significantly shorter survival than those who relapsed later (OS 7 vs. 41 months; p<0.05).

Comment: Mantle cell lymphoma has been considered an incurable disease and associated with poor survival outcomes. Before the introduction of the monoclonal CD20 antibody rituximab in the late 1990s, the median first-line OS of patients with mantle cell lymphoma was 2–3 years. This report from centres in Finland and Spain analyses the survival of 564 real-world patients with mantle cell lymphoma diagnosed between 2000-20. They report a 2-year OS of 77%, a 5-year OS of 58% and a 10-year OS of 32%, with an estimated median OS of 80 months. Clearly, in addition to the introduction of rituximab, the intensive nature of current therapy, including high-dose cytarabine, and high-dose chemotherapy and autologous transplantation, has played an important role in these improved outcomes. However, the outcomes in non-transplant eligible patients, even in those greater than 75 years of age, have also improved with a median OS of 37 months and disease-specific survival of 54 months. One of the most significant results from the analysis is that early relapse within 24 months of completing first-line treatment was associated with statistically significant worse survival compared to later relapse, analogous to progression of disease within 24 months in follicular lymphoma.

Reference: Br J Haematol. 2023;201(1):64-74
Abstract

Nelarabine combination therapy for relapsed or refractory T-cell acute lymphoblastic lymphoma/leukemia

Authors: Shimony S et al.

Summary: These researchers compared the efficacy and toxicity of nelarabine (an antimetabolite prodrug) in 44 adult and paediatric patients (median age 19 years; 18 children) with relapsed or refractory T-cell acute lymphoblastic leukaemia and lymphoma (R/R T-ALL/LBL) as either combination therapy (n=29; 76% with cyclophosphamide and etoposide) or monotherapy (n=15). A total of 24 patients (55%) achieved complete remission after a median of 1 cycle (range 1-3) of treatment. A numerically higher proportion of patients who received nelarabine combination therapy achieved remission than monotherapy (62% vs. 40%), however this did not reach statistical significance (p=0.21). Across the entire cohort, OS was 12.8 months (95% CI 6.93—not reached), and 24-month OS was higher for patients who received combination therapy than monotherapy (52.9% vs. 8.2%; p=0.0026). Combination therapy was associated with higher rates of grade 3/4 thrombocytopenia (66% vs. 27%; p=0.014) and anaemia (76% vs. 20%; p<0.001), however neurotoxicity rates were comparable between treatment groups (27% vs. 17%; p=0.46). Allogenic stem cell transplant was undertaken by 88% of responders. Multivariate analyses revealed that OS was improved with combination therapy (HR 0.41; p=0.04) and by allogenic stem cell transplant following nelarabine (HR 0.25; p=0.008).

Comment: T-ALL/LBL comprises approximately 15% of ALL cases and most commonly occurs in adolescent and young adult males. Whilst the cure rate is high, the outcome of relapsed disease is dismal. This study reports on the experience of 44 patients at 3 centres of nelarabine and nelarabine combination regimens in adults and paediatric patients with relapsed/refractory disease. Combination therapy was with cyclophosphamide and etoposide (NECTAR). The group who received combination therapy (n=29) had a greater CR rate than those who received monotherapy (n=15), 62% versus 40%, although this was not statistically significant. However, patients receiving combination therapy did have statistically significantly higher OS than those receiving monotherapy (24-month OS 52.9% vs 8.2%; p=0.0026). Additionally, the combination therapy was well tolerated and associated with a toxicity profile comparable to monotherapy. The importance of this data is the role of nelarabine in bridging patients to allogeneic transplant which is essential for cure in these patients.

Reference: Blood Adv. 2023;7(7):1092-102
Abstract

Decitabine versus hydroxyurea for advanced proliferative chronic myelomonocytic leukemia

Authors: Itzykson R et al.

Summary: This paper reports the results of a phase 3 trial within the EMSCO network, which randomised patients newly diagnosed with advanced myeloproliferative chronic myelomonocytic leukaemia (MP-CMML) to either decitabine (n=84) or hydroxyurea (n=86). At a median follow-up of 17.5 months, patients who received decitabine had numerically higher EFS than hydroxyurea (primary endpoint; 17.5 vs. 12.1 months), however this did not reach statistical significance (p=0.27). A higher proportion of patients in the decitabine arm achieved a response than hydroxyurea (63% vs. 35%; p=0.0004), however median duration of response and median OS were comparable between arms ([16.3 vs. 17.4 months; p=0.90] and [18.4 vs. 21.9 months; p=0.67], respectively). There were no associations between treatment effect and CMML Prognostic Scoring System risk, Group Francophone des Myelodysplasies, anaemia, platelet or blast count.

Comment: The myeloproliferative subset of CMML (MP-CMML), defined by a white blood cell count ≥ 13 x 10^9/L represents 40-50% of patients with CMML and is associated with a poor prognosis and, for those who are ineligible for a transplant, cytoreduction remains standard of care. Phase 3 studies in this disease are few and far between, so this was a rare and interesting randomised phase 3 study comparing hydroxyurea and decitabine (5 days per month intravenous course). Whilst the overall response rate of 63% with decitabine was clearly superior to that seen with hydroxyurea (35%), there was no difference in EFS or OS. This was accounted for by the higher response rate of decitabine being offset by increased toxicity, notably of infectious or cardiovascular origin. In Australia, intravenous decitabine is not approved, but the oral form of decitabine administered with the cytidine deaminase inhibitor, cedazuridine, was approved by the TGA in October 2020, and is now listed on the PBS for MDS, CMML and low bulk AML. Whilst the results of trials with the intravenous preparation of decitabine cannot necessarily be translated to the oral decitabine/cedazuridine combination, this study confirms that hydroxyurea is a valid treatment option, especially in older transplant-ineligible patients.

Reference: J Clin Oncol. 2023;41(10):1888-97
Abstract

DNA sequencing to detect residual disease in adults with acute myeloid leukemia prior to hematopoietic cell transplant

Authors: Dillon LW et al.

Summary: The objective of this retrospective observational study was to evaluate whether DNA sequencing of blood from 1075 patients with acute myeloid leukaemia (AML) in first remission prior to allogeneic hematopoietic cell transplant could identify those at increased risk of relapse and poorer survival. In the discovery cohort of 371 patients, the persistence of *NPM1* and/or *FLT3* internal tandem duplication variants at an allele fraction of 0.01% or higher prior to transplantation were associated with poorer outcomes after transplantation. In the validation cohort of 451 patients who had undergone transplant, residual of *NPM1* and/or *FLT3* internal tandem duplication variants were associated with higher rates of relapse at 3 years (68% vs. 21%; p<0.001) and poorer survival at 3 years (39% vs. 63%; p<0.001).

Comment: In this study, investigators used next-generation sequencing to screen blood samples from 1075 adults in remission from AML who were preparing for allograft. In total, 822 patients had *NPM1* and/or *FLT3* internal tandem duplication variants present at their initial AML diagnosis. Investigators found that 142 adults were measurable residual disease (MRD) positive after therapy (defined as an allele fraction of 0.01% or higher). Three years following bone marrow transplant, nearly 70% of these patients relapsed while 39% survived. In comparison, 21% of adults who were MRD negative at time of transplant relapsed after 3 years, while 63% survived. Of note, these were blood samples and it is not known how next-generation sequencing MRD testing on bone marrow would differ from blood. Also, other potential next-generation sequencing-MRD targets (*FLT3-TKD, IDH1, IDH2*) were not selected for validation. The results show that approximately 1 in 6 patients are in a high-risk subgroup with MRD detectable higher than 0.01%, with serious posttransplant outcomes not adequately addressed by the current clinical standard of care.

Reference: JAMA. 2023;329(9):745-55
Abstract

Venetoclax plus azacitidine compared with intensive chemotherapy as induction for patients with acute myeloid leukemia

Authors: Zeidan AM et al.

Summary: The treatment outcomes of venetoclax plus azacitidine versus intensive chemotherapy for AML were compared in this retrospective analysis of an electronic medical record database in the US. A total of 276 patients were identified and propensity score-matched. Compared to venetoclax plus azacitidine, patients who received intensive chemotherapy had higher rates of CR (60.9% vs. 44.2%; p=0.006) and hematopoietic stem cell transplant (HSTC; 18.1% vs. 8.0%; p=0.012), however no statistically significant differences in OS or RFS were observed between the two treatment groups, with or without censoring. The authors note that randomised controlled trials are needed to effectively compare the two treatment regimens.

Comment: This paper presents a real-world retrospective analysis comparing venetoclax plus azacitidine with intensive chemotherapy as induction for patients with AML. While CR and HSCT rates were higher with intensive chemotherapy (60.9% and 18.1% vs. 44.2% and 8.0%), no significant differences were observed in OS or RFS between the two arms. Of note, the HSCT rate of 18.1% is quite low in the intensive chemotherapy group compared to clinical standards. This study did conduct propensity-score matching in a 1:1 ratio between the two cohorts to address potential confounding due to large differences in baseline characteristics. As venetoclax plus azacitidine is approved for patients who are ineligible for intensive chemotherapy or aged ≥75 years, the propensity-score matching may have selected patients in the intensive chemotherapy group who were less likely to receive HSCT.

Reference: Ann Hematol. 2023;102(4):749-54
Abstract

Survival of *TP53*-mutated acute myeloid leukemia patients receiving allogeneic stem cell transplantation after first induction or salvage therapy

Authors: Badar T et al.

Summary: This paper reports on results from the Consortium on Myeloid Malignancies and Neoplastic Diseases (COMMAND), which investigated factors that predict survival in patients with *TP53*-mutated AML undergoing allogeneic haematopoietic stem cell transplant (allo-HSCT). Among a total of 370 patients with *TP53*-mutated disease, 68 (18%) were bridged to allo-HSCT. Patients had a median age of 63 years, 66% had multi-hit *TP53*-mutations and 82% had complex cytogenetics. Myeloablative conditioning was administered to 43% and intensity conditioning to 57%. Acute GVHD and chronic GVHD had incidences of 37% and 44%. Following allo-HSCT, median EFS was 12.4 months and median OS 24.5 months. Multivariate analyses revealed that complete remission 100 days following allo-HSCT was associated with improved EFS (HR 0.24; p=0.001) and OS (HR 0.22; p≤0.001). Chronic graft versus host disease was also associated with improved EFS (HR 0.21; p≤0.001) and OS (HR 0.34; p=0.007).

Comment: *TP53*-mutated AML is associated with high relapse rate and poor OS. While allogeneic HSCT is a potential curative option for high-risk AML, earlier reports demonstrated a lack of benefit of this therapy in patients with *TP53*-mutated AML. This is a multi-centre study that explores factors predicting survival for these patients undergoing allogeneic HSCT. Out of 370 *TP53*-mutated AML patients, 68 (18%) patients were bridged to transplant. Despite the earlier reports, this study suggests that allo-HSCT is associated with improved long-term outcomes. In multivariate analysis, significant improvement in survival was observed among patients who were in complete remission at day 100 post allo-HSCT or had chronic GVHD. Interestingly, unlike other studies that have shown that conditioning intensity is important, this study did not observe a significant association between conditioning intensity and outcomes in this cohort, emphasising the importance of the graft versus leukaemia effect.

Reference: Leukemia. 2023;37(4):799-806
Abstract

Lymphoma & Leukaemia Research Review™

Independent commentary by Associate Professor Stephen Larsen

Stephen Larsen is a clinical haematologist at Royal Prince Alfred Hospital in Sydney. He has an interest in haematological malignancies and haematopoietic stem cell transplantation and is the head of the transplant unit at RPAH. He is actively involved in clinical trials in lymphoma, leukaemia and transplantation.