Lymphoma & Leukaemia Research Review™

Making Education Easy

Issue 81 - 2023

In this issue:

Abbreviations used in this issue:

ATG = antithymocyte globulin; **B-ALL** = B-cell acute lymphocytic leukaemia; **BV + AVD** = brentuximab vedotin plus doxorubicin, vinblastine and dacarbazine; **DLBCL** = diffuse large B-cell lymphoma; **HGBL** = high-grade B-cell lymphoma; **HMA** = hypomethylating agents; **PN** = peripheral neuropathy; **PTCy** = post-transplant cyclophosphamide; **SF** = splicing factor.

Welcome to issue 81 of Lymphoma & Leukaemia Research Review.

This review begins with an open-label, phase 2 study that evaluated the efficacy of axi-cel in relapsed/refractory large B-cell lymphoma patients, and whether it is an appropriate second-line treatment. Another interesting study assessed whether intensive chemotherapy can be replaced with decitabine monotherapy in acute myeloid leukaemia patients, and if it has a superior safety profile. This review concludes with a paper that determined the role of consolidative radiotherapy in residual fluorodeoxyglucose activity, and if it's activity could increase the risk of local progression.

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

Kind Regards,

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Axicabtagene ciloleucel as second-line therapy in large B cell lymphoma ineligible for autologous stem cell transplantation: a phase 2 trial

Authors: Houot R et al.

Summary: In the ALYCANTE, open-label, phase 2 study, the efficacy of axi-cel as second-line treatment, compared to standard of care, was investigated. R/R large B-cell lymphoma patients were included, 62 of which were ineligible for ASCT. After analysis, a complete metabolic response of 71.0% was obtained (95% CI 58.1 to 81.8%) at 3 months, and after a median follow-up of 12.0 months, a PFS of 11.8 months was achieved (8.4-not reached). An OS was not reached and there was no unexpected toxicity. 8.1% of patients had cytokine release syndrome and 14.5% had neurologic events of grade 3 to 4. Overall, these results suggest that axi-cel could be an appropriate second-line therapy for those who are ineligible for ASCT.

Comment: Axi-cel is a CD19 directed CAR T-cell therapy which was shown to be superior to ASCT as second line therapy for relapsed DLBCL in the pivotal ZUMA 7 randomised study. This phase 2 study from French investigators examined axi-cel in a cohort of patients deemed unfit for ASCT and for whom the treatment would historically be palliative chemotherapy, achieving an encouraging CMR rate of 71% at 3 months with an expected rate of CAR T related toxicities (CRS 8.1% and neurotoxicity 14.5%). A non-relapse mortality of 9.7% (6 of 62 patients), all due to infection is a reminder about the importance of mitigation strategies such as judicious antimicrobial prophylaxis and IVIG use. Axi-cel is currently funded only in the 3rd line setting in Australia.

Reference: Nat Med. 2023;29(10):2665.
Abstract

Sequential CD19 and CD22 chimeric antigen receptor T-cell therapy for childhood refractory or relapsed B-cell acute lymphocytic leukaemia: a single-arm, phase 2 study

Authors: Pan J et al.

Summary: Within this single-centre, phase 2 trial based in China, the activity and safety of sequential CD19-directed and CD22-directed CAR T-cell treatments in children with R/R B-cell acute lymphocytic leukaemia (B-ALL) was investigated. Patients were aged 1-18 years with a CD19 and CD22 positivity greater than 95%. They each received CD19-directed CAR T-cells intravenously followed by a CD22-directed infusion. Eighty-one patients were included (38% female, median age 8 years), with all 81 receiving the first infusion and 79 received the sequential infusions. The median dose for CD19-directed was 2.7x106 per kg and 2.2x106 per kg for CD22-directed, with a median interval of 39 days between infusions. Sixty-two patients had the target dose, with 60 (97%, 95% CI 89 to 100) achieving the objective response. Of those receiving the target dose, their 18-month event-free survival was 79% (66 to 91), length of remission was 80% (68 to 92), OS was 96% (91 to 100) and disease-free survival was 80% (68 to 92). Common grade 3 or 4 AEs were cytopenias, cytokine release syndrome, neurotoxicity, and infections. Results suggest that this sequential strategy could provide long-term benefits for this patient population.

Comment: Although CD19 directed CAR T-cell therapy has dramatically improved outcomes in patients with B-ALL, relapsed disease is a known complication that frequently occurs due to the growth of antigen negative clones, with the loss or downregulation of CD19. Various strategies have been hypothesised to reduce this mechanism of immune escape, including tandem or bicistronic CAR products that target two separate antigens. This study from China utilised sequential CD19 and CD22 CAR T-cell infusions for relapsed B-ALL, with the second infusion given once MRD negative remission was attained and toxicities were no longer severe. Although response rates were impressively high with most maintained at a median follow up of 18 months, the rate and nature of any further relapses (including antigen expression) with longer term follow up are important in determining the benefit of this approach over CD19 CAR T-cell therapy alone.

Reference: Lancet Oncol. 2023;24(11):1229-1241.
Abstract

Tolerability and efficacy of the anticluster of differentiation 47 antibody magrolimab combined with azacitidine in patients with previously untreated AML: Phase Ib results

Authors: Daver NG et al.

Summary: This is a final report on the phase Ib data that aimed to determine the efficacy of magrolimab plus azacitidine in untreated AML patients that were not eligible for intensive chemotherapy. Patients included (n=87) received 1mg/kg of magrolimab on days 1 and 4 followed by 15mg/kg on day 8 and 30mg/kg once weekly or every 2 weeks for maintenance, as well as azacitidine (75mg/m^2) on days 1-7 of each 28-day cycle. Seventy-two patients had *TP53* mutations (median variant allele frequency: 61%), with 79.2% having European LeukamiaNet 2017 adverse-risk cytogenetics. Common treatment-emergent AEs were constipation (49.4%), nausea (49.4%) and diarrhoea (48.3%), with 30 (34.5%) patients experiencing anaemia. There was a median haemoglobin change from baseline to post dose assessment of -0.9 g/dL (range -3.6 to 2.5 g/dL). A CR was obtained by 28 patients, 23 of which had *TP53* mutations, and *TP53*-mutant patients achieved an OS of 9.8 months versus 18.9 months for wild-type patients, respectively. Overall, magrolimab plus azacitidine was generally well tolerated, and had a promising efficacy.

Comment: Magrolimab is a macrophage checkpoint inhibitor targeting CD47 that is being studied in myeloid malignancies, with pre-clinical data suggesting synergy when combined with azacitidine, which can upregulate phagocytic signals on leukaemia cells. This is a phase I study of magrolimab and azacitidine in patients with untreated AML, with a CR rate of 32% with very similar responses in the subset of patients with *TP53* mutations, which historically have poor outcomes. Early anaemia was a recognised toxicity that required mitigation strategies, including enhanced monitoring. Unfortunately, pivotal phase 3 studies of magrolimab in AML and MDS have been paused and has raised questions over the field of CD47 targeting agents and their future in this disease group.

Reference: J Clin Oncol. 2023;1;41(31):4893-4904.
Abstract

Posttransplant cyclophosphamide versus antithymocyte globulin in patients with acute lymphoblastic leukemia treated with allogeneic hematopoietic cell transplantation from matched unrelated donors: A study from the acute leukemia working party of the European society for blood and marrow transplantation

Authors: Giebel S et al.

Summary: Within this retrospective study, researchers compared the use of antithymocyte globulin (ATG) to post-transplant cyclophosphamide (PTCy) as a prophylaxis graft for ALL patients. Patients included received PTCy (n=117) or ATG (n=779) and had a median age of 40 and 43 years, respectively. After a univariate analysis, it was identified that patient's cumulative incidence of acute and chronic graft-versus-host disease were similar for both groups, however, the incidence decreased after 2 years for those in the PTCy group (18% versus 25%, p=0.046) and there was no large impact on non-relapse mortality (11% versus 16% in the ATG group, p=0.29). Leukaemia-free survival rate was 71% (PTCy) versus 59% (ATG) (p=0.01), and OS was 82% versus 74% (p=0.08), respectively. A reduced risk of extensive chronic graft-versus-host disease was reported for ATG patients, when compared to PTCy (HR 0.54, 95% CI 0.3 to 0.98, p=0.04), as well as an increased risk for low leukaemia-free survival (1.57, 1.01 to 2.45, p=0.045). Overall, results suggest that ATG compared to PTCy is associated with inferior leukaemia-free survival, however, warrants further investigation.

Comment: The use of PTCy as a graft versus host disease prophylaxis platform has revolutionised haplo-identical stem cell transplantation and is now increasingly being used in other scenarios, including matched donor transplantation. This retrospective EBMT analysis compared PTCy to ATG, another commonly used in vivo T-cell depletion strategy, for patients with ALL receiving a transplant from a fully matched unrelated donor in first remission. Outcomes were improved in the PTCy arm, perhaps surprisingly driven by a lower risk of leukaemia relapse compared with ATG, albeit with a higher risk of chronic GVHD. The usual caveat to retrospective analysis applies to such findings, and there is a need for prospective randomised data comparing ATG and PTCy.

Reference: Cancer. 2023;1;129(23):3735-3745.
Abstract

Launched in September, the Leukaemia Foundation and Tour de Cure partnered to announce the inaugural Breakthrough Research Fellowship program – one of the most significant investments into blood cancer research the Leukaemia Foundation has made.

The Breakthrough Fellowship will enable the two recipients to lead and shape blood cancer research in the future in Australia, with both the Leukaemia Foundation and Tour de Cure pledging $2million each to the program.

The inaugural recipients of the Breakthrough Fellowship are:

Dr Ashley Ng – Uncovering the secrets behind leukaemia treatment resistance

Dr Ng's innovative research project, Igniting Progress in B-ALL: Elucidating Resistance Mechanisms and Pioneering Therapies, will be conducted over five years at WEHI.

He seeks to pioneer the future of blood cancer treatment by lifting the molecular lid on how blood cancer resists current medicines, with a focus on acute lymphoblastic leukaemia (ALL).

Dr Ashwin Unnikrishnan – Replacing 'blunt-edged' chemotherapy with targeted treatment

His research project, Skipping beyond chemotherapy: Therapeutically targeting aberrant RNA splicing in Acute Myeloid Leukaemia, will be conducted over five years at UNSW, and aims to provide new treatment options for people diagnosed with AML where standard treatment has failed.

"The standard treatment for AML is chemotherapy, a blunt-edged tool that kills cells indiscriminately whilst being ineffective at eliminating leukaemic cells from the body," said Dr Unnikrishnan.

"Our proposal aims to improve this by discovering more specific and effective ways to kill leukaemia cells."

For more information on the Breakthrough Fellowship Program, please go to https://www.leukaemia.org.au/research/current-funding-opportunities/breakthrough-fellowship/

10-day decitabine versus 3 + 7 chemotherapy followed by allografting in older patients with acute myeloid leukaemia: an open-label, randomised, controlled, phase 3 trial

Authors: Lübbert M et al.

Summary: This open-label, randomised, phase 3 controlled trial investigated whether intensive chemotherapy can be replaced with decitabine monotherapy in AML patients. Fifty-four hospitals located in 9 European countries were included, involving 606 patients aged 60 years or older that were newly diagnosed with AML. Patients were randomly allocated (1:1) to receive either decitabine (n=303) or standard chemotherapy (n=303). After a median follow-up of 4.0 years, patient's OS was 26% within the decitabine group (95% CI 21 to 32) versus 30% in the chemotherapy group (24 to 35) (HR for death 1.04, 95% CI 0.86 to 1.26, p=0.68). Patients obtained a similar rate of on-protocol allogeneic HSCT (122 [40%] decitabine patients and 118 [39%] chemotherapy patients), and the rate of grade 3-5 AEs were 254/302 (84%) within the decitabine group compared to 279/298 (94%) in the chemotherapy group. Grade 3-5 infections (41% [125 of 302] versus 53% [158 of 298]), oral mucositis (2% [7 of 302] versus [31 of 298]) and diarrhoea (1% [3 of 302] versus 8% [24 of 298]) were lower for those in the decitabine group. Results suggest that decitabine could have a better safety profile than intensive chemotherapy.

Comment: Hypomethylating agents (HMA) are a valuable option for the treatment of AML, traditionally for patients who are not fit for intensive chemotherapy, with a low blast burden. This prospective multicentre randomised trial compared decitabine with intensive chemotherapy in older patients with AML eligible for intensive chemotherapy. Although the response rates were comparable and a good proportion of patients in both arms proceeded to ASCT, the use of single agent HMA has largely been supplanted by combinations with the BCL2 inhibitor venetoclax. There are several ongoing trials comparing the low intensity approach of HMA and venetoclax with intensive chemotherapy across groups including fit older patients, with results eagerly awaited.

Reference: Lancet Haematol. 2023;10(11):e879-e889.
Abstract

Venetoclax abrogates the prognostic impact of splicing factor gene mutations in newly diagnosed acute myeloid leukemia

Authors: Senapati J et al.

Summary: In this study, researchers aimed to determine the impact of mutations in splicing factor (SF) genes in AML patients. 994 patients (median age 67 years) that had newly diagnosed AML were included for analysis, 266 of which had a SF^{mut}, and were generally older than 72 years (most common SF^{mut}: SRSF2 [n=140, 53%]). It was identified that patients who were treated with intensive therapy and had a SF^{mut} had a shorter relapse-fee survival (9.6 versus 21.4 months, p=0.04) and OS (15.9 versus 26.7 months, p=0.06) compared to those without a SF^{mut}, however, this significance abrogated when analysing those who received venetoclax plus intensive therapy (relapse-free survival 15.4 versus 20.3 months, p=0.036; OS 19.6 versus 30.7 months, p=0.98). Patients who were treated with LI obtained a median relapse-free survival (9.3 versus 7.7 months, p=0.35) and OS (12.3 versus 8.5 months, p=0.14) similar to patients with and without a SF^{mut}, with all patient's outcomes improving when receiving venetoclax. Further studies are warranted that consider both LI therapy and venetoclax.

Comment: Genetic testing with the use of next generation sequencing is now funded in Australia in the diagnostic workup of newly diagnosed AML, and important in prognostication as noted in the widely used ELN 2022 classification of AML. Splicing gene mutations which are enriched in AML that is therapy related and with myelodysplasia related changes, are considered adverse risk in the ELN classification. This single centre retrospective analysis examined the outcomes of a cohort of patients with spicing mutations treated with intensive chemotherapy and lower intensity venetoclax based regimens, with the latter resulting in treatment outcomes that were similar to patients without these mutations. Although such results are hypothesis generating, it suggests that risks stratification in AML will increasingly need to incorporate the effect of the broadening armamentarium of leukaemia treatments in addition to biological characteristics.

Reference: Blood. 2023;9;142(19):1647-1657.
Abstract

Lenalidomide plus rituximab for the initial treatment of frail older patients with DLBCL: the FIL_ReRi phase 2 study

Authors: Gini G et al.

Summary: This phase 2, Italian study investigated the activity and safety of rituximab plus lenalidomide in untreated, frail DLBCL patients that were 70 years or older. Patients received 6 28-day cycles of oral lenalidomide (20mg) from days 2 to 22 as well as IV rituximab (375mg/m3) on day 1. Those who obtained a partial response or CR at cycle 6 received lenalidomide (10mg/d) on days 1 to 21 for every 28 cycles, for 12 total cycles. After analysis, an ORR of 50.8% was obtained, with a CR of 27.7%. Median follow-up was 24 months, and PFS was 14 months, with a 2-year duration of response of 64%. Extra haematological toxicity occurred in 34 patients, as deemed by the national cancer institute common terminology criteria for AEs grade ≥3. These results highlight the need for further exploration in a chemo-free approach for this patient population.

Comment: The median age of diagnosis of DLBCL is 70, and the treatment of older frail patients remains a challenge. The complications of chemotherapy, including anthracycline induced cardiotoxicity, is a concern in this often-comorbid patient population. This Italian phase 2 study prospectively identified frail patients over 70 who were treated with 6 cycles of rituximab and lenalidomide (R2). This is a commendable study given the challenges of completing trials in this patient population, though the modest response rates (51% ORR and 28% CR) and not inconsiderable toxicities suggest that this regimen is unlikely to routinely challenge the R-miniCHOP backbone for frontline treatment in older frail patients.

Reference: Blood. 2023;26;142(17):1438-1447.
Abstract

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Independent commentary by Dr Shafqat Inam

Dr Shafqat Inam is a consultant haematologist and BMT physician at the Alfred Hospital. He has an interest in allogeneic stem cell transplantation, and the role of novel cell and immune therapies including CAR T cell therapy in the treatment of lymphoma, leukaemia, and myeloma.

High-grade B-cell lymphoma, not otherwise specified: a multi-institutional retrospective study

Authors: Zayac AS et al.

Summary: The characteristics and outcomes of high-grade B-cell lymphoma (HGBL), not otherwise specified, patients were evaluated in this multi-institutional retrospective study. From those included, 83% had a germinal centre B-cell immunophenotype and 37% had a dual-expressor immunophenotype (MYC and BCL2 expression), with 28% having MYC rearrangement, 13% having BCL3 rearrangement and 11% having BCL6 rearrangement. Majority of patients had stage IV disease, high serum lactate dehydrogenase levels, as well as other high-risk clinical factors. Common first-line regimens were dose-adjusted cyclophosphamide, doxorubicin, vincristine and etoposide with rituximab plus prednisone (43%), rituximab, cyclophosphamide, doxorubicin, vincristine plus prednisone (33%) or other intensive chemotherapy. No significant differences in CR, PFS or OS were observed between chemotherapy regimens. Furthermore, 69% of patients attained a CR, with a PFS and OS at 2 years of 55.2% and 68.1%. Prognostic factors were poor performance status, lactate dehydrogenase >3 x upper limit of normal and dual expression immunophenotypes. An improved diagnostic criteria and therapeutic approach is warranted to overcome unfavourable prognoses for this patient population.

Comment: HGBL, not otherwise specified, is a new category in the classification of aggressive lymphomas, defined as having blastoid morphology but without double hit cytogenetics. Given the relative rarity of this subtype, this useful retrospective multicentre review of cases highlights several pertinent characteristics: the high rate of double expressor (MYC and BCL2) phenotype, the lack of prognostic impact of MYC rearrangements and the very poor outcomes with *TP53* alterations. Interestingly, there was no benefit found in the use of the infusion regimen of DA-EPOCH-R over standard R-CHOP, suggesting alternate approaches incorporating newer immunotherapies are needed to overcome the poor outcomes of this subtype.

Reference: Blood Adv. 2023;14;7(21):6381-6394.
Abstract

Brentuximab vedotin plus AVD for Hodgkin lymphoma: incidence and management of peripheral neuropathy in a multisite cohort

Authors: Bowers JT et al.

Summary: This study aimed to characterise peripheral neuropathy (PN) in patients with stage III/IV classical Hodgkin lymphoma that have received brentuximab vedotin plus doxorubicin, vinblastine and dacarbazine (BV + AVD). Utilising a multisite, retrospective study, 153 patients from 10 US institutions were included. After analysis, 80% of patients reported PN whilst receiving treatment (39% grade 1, 31% grade 2 and 10% grade 3), with 44% of patients modifying BV due to PN, leading to 23% of patients to discontinue treatment, 17% had a dose reduction and 4% had a temporary hold of treatment. Patients obtained a median follow-up of 24 months, with 36% of patients reporting PN resolution and 33% reporting improvements at their last follow-up. Furthermore, a 2-year PFS of 82.7% (95% CI 0.76 to 0.90) and OS of 97.4% (0.94 to 1.00) was achieved. Overall, results suggest that BV + AVD could be associated with an increased incidence of PN.

Comment: BV is a potent antibody drug conjugate targeting CD30 that is active against Hodgkin lymphoma, most often used in the relapsed setting in Australia due to lack of reimbursement for upfront treatment. The main limiting toxicity is PN, which can have significant impairment of QoL and functional capacity in a disease which frequently affects young working age adults. This real-world multicentre analysis found a high rate of PN leading to dose reduction or treatment discontinuation, though no reported impact on PFS in those who discontinued BV. This is useful data when counselling patients to obtain informed consent for commencing this agent.

Reference: Blood Adv. 2023;14;7(21):6630-6638.
Abstract

Consolidative radiotherapy for residual fluorodeoxyglucose activity on day +30 post CAR T-cell therapy in non-Hodgkin lymphoma

Authors: Saifi O et al.

Summary: Within this study, the role of consolidative radiotherapy for residual fluorodeoxyglucose activity 30 days or more after CAR T-cell therapy in non-Hodgkin lymphoma patients was evaluated. Patients (n=61) were retrospectively reviewed, determining their PFS, OS and local relapse-free survival. After day +30 and a PET scan, 45 patients were observed and 16 received consolidative radiotherapy. A spontaneous CR was obtained by 15 patients that were observed, with 27 (60%) progressing with all relapses involving initial sites of residual fluorodeoxyglucose activity, compared to patients receiving consolidative therapy, where 10 (63%) achieved a CR and 4 (25%) progressed, none of which were in the irradiated sites. Two-year local relapse-free survival was 100% for consolidative sites and 31% in observed sites (p<0.001), with a 2-year PFS of 73% and 37% (p=0.025) and OS of 78% and 43% (p=0.12), respectively. These findings suggest that those with residual fluorodeoxyglucose activity after CAR T-cell therapy could have an increased risk of local progression.

Comment: PET CT scans are frequently done at about day 30 following CAR T-cell therapy for non-Hodgkin lymphoma to assess treatment response. Although some patients with partial response at this timepoint convert to CRs as this 'living drug' continues to expand and work, many have progressive disease (very few patients with DLBCL with Deauville 5 disease will achieve remission). Better strategies are needed to improve outcomes for patients receiving this expensive and effort intensive therapy. This retrospective review of patients who receive consolidative radiotherapy to sites of persistent disease at day 30 showed superior outcomes to those patients who did not, suggesting a proactive approach to residual PET avid disease. More sensitive methods to detect patients likely to relapse such as detection of circulating tumour DNA, and combination pre-emptive strategies utilising modalities including radiotherapy and novel immunotherapies, such as bispecific antibodies, will hopefully improve outcomes.

Reference: Haematologica. 2023;1;108(11):2982-2992.
Abstract

