Malignant Haematology
RESEARCH REVIEW™

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Issue 10 – 2025

In this issue:

Abbreviations used in this issue

AML = acute myeloid leukaemia
CAR = chimeric antigen receptor
CR/PR/VGPR = complete/(very good) partial response
ENKTL = extranodal natural killer/T-cell lymphoma
GVHD = graft-versus-host disease
HR = hazard ratio
MCL = mantle cell lymphoma
MM = multiple myeloma
MRD = minimal residual disease
OS = overall survival
PD-1/PD-L1 = programmed cell death (ligand)-1
PFS = progression-free survival
SCT = stem-cell transplantation

Welcome to the tenth issue of Malignant Haematology Research Review.

We begin this issue comparing the impact of the eBEACOPP (escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) and BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone) regimens on fertility outcomes when used for patients with advanced-stage classical Hodgkin lymphoma. There is also research from the Mayo Clinic reporting on 15-year trends in autologous SCT utilisation, factors that have influenced practice changes, and current indications amid newer therapies for patients with AL (light-chain) amyloidosis. Final results from the phase 3 BELLINI trial of adding venetoclax to bortezomib and dexamethasone for relapsed or refractory MM are also presented, and they highlight the importance of good trial design. The issue concludes with results from isatuximab-carfilzomib-lenalidomide-dexamethasone induction in the MIDAS study, which is assessing an MRD-driven consolidation and maintenance strategy after this induction regimen.

We value your comments and feedback, so please keep sending them.

Kind regards,

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Fertility in patients with advanced-stage classic Hodgkin lymphoma treated with BrECADD versus eBEACOPP

Authors: Ferdinandus J et al.

Summary: This secondary analysis of the open-label, randomised phase 3 HD21 trial analysed gonadal function recovery and fertility outcomes for 4–6 cycles of eBEACOPP versus BrECADD in 420 male and 347 female participants of childbearing potential with newly diagnosed, advanced-stage classical Hodgkin lymphoma. Compared with eBEACOPP, BrECADD was associated with a significantly higher 4-year gonadal function recovery rate in women (95.3% vs. 73.3%; HR 1.69 [95% CI 1.34, 2.14]) and men (85.6% vs. 39.7%; 3.28 [2.51, 4.30]), with generally higher anti-Müllerian hormone and inhibin B levels among BrECADD recipients. The 5-year incidence of parenthood was significantly higher for male BrECADD recipients than male eBEACOPP recipients (9.3% vs. 3.3% [p=0.014]), but not female BrECADD recipients compared with female eBEACOPP recipients (19.3% vs. 17.1% [p=0.53]).

Comment (LB): While ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) is associated with lower gonadotoxicity, it has demonstrated inferior disease control compared with eBEACOPP in advanced-stage classical Hodgkin lymphoma. As patients with Hodgkin lymphoma are often wanting to start or continue a family, the need to preserve fertility after treatment is highly desired and forms a large part of the pretransplant counselling and management. The gonadal toxicity in eBEACOPP comes from the procarbazine. Substitution of procarbazine with dacarbazine in the BrECADD arm has allowed a significant increase in the number of women who retain their fertility as measured by FSH (follicle-stimulating hormone) levels <25 mIU/mL. Women assigned to BrECADD had significantly higher 4-year gonadal function recovery rates compared with those receiving eBEACOPP (95.3% [95% CI 92.0, 98.8] vs. 73.3% [66.9, 80.4]; HR 1.69). Male outcome was similar. In women, the greatest benefit in terms of gonadal function recovery with BrECADD over eBEACOPP was observed in those aged 30 years or older (86.2% [95% CI 77.5, 95.9] vs. 46.4% [35.4, 60.8]; HR 2.92). Overall in the HD21 study, there were 108 reported childbirths (73 to female participants [one stillbirth]; 35 to partners of male participants) in 99 patients; 59 in the BrECADD group and 40 in the eBEACOPP group. During follow-up, 92 pregnancies were reported among female patients. The median age at first pregnancy was 27 years (IQR 24–30) with BrECADD and 25 years (22–28) with eBEACOPP. I was interested to note that 87 (95%) of the 92 pregnancies occurred without using cryopreserved material, and 73 (79%) of the 92 pregnancies resulted in childbirth. Overall, the gonadotoxic potential of BrECADD seems to be similar to that of the ABVD regimen. Rates of fertility after ABVD in the RATHL study (treating similar populations) were similar to those in the BrECADD arm. Many NZ haematologists are now treating high-risk disease, e.g. IPS score 4 or greater, with eBEACOPDAC, substituting procarbazine with dacarbazine. This protocol is widely used in the UK and other countries where brentuximab is not available for first-line treatment.

Reference: Lancet Oncol 2025;26:1081–90

Abstract

Graft-versus-host disease prophylaxis with cyclophosphamide and cyclosporin

Authors: Curtis DJ et al., for the Australasian Leukaemia and Lymphoma Group

Summary: Adults undergoing SCT from a matched related donor after myeloablative or reduced-intensity conditioning were randomised to post-transplantation GVHD prophylaxis with cyclophosphamide-ciclosporin (n=66) or standard prophylaxis with ciclosporin-methotrexate (n=68). Compared with standard prophylaxis, cyclophosphamide-ciclosporin was associated with significantly longer median GVHD-free, relapse-free survival (primary endpoint; 26.2 vs. 6.4 months [p<0.001]) with a greater 3-year rate of this outcome (49% vs. 14%; HR 0.42 [95% CI 0.27, 0.66]), as well as a lower 3-month cumulative grade III–IV acute GVHD incidence (3% vs. 10%) and a numerically higher 2-year OS rate (83% vs. 71%; HR for death, 0.59 [95% CI 0.29, 1.19]). The two groups had similar incidences of serious adverse events during the first 100 days post-transplantation.

Comment (LB): The holy grail of allogeneic transplant is to separate GVHD from graft-versus-leukaemia. Ciclosporin-methotrexate has been the cornerstone of post-transplant GVHD prophylaxis for decades. Adding T-cell depletion reduces acute and especially chronic GVHD, but at the expense of more relapse, so it is only appropriate for certain high-risk situations. Post-transplant cyclophosphamide has also been around for years, but this ALLG study has cemented its role in matched donor transplants. There was a reduction in severe acute GVHD (3% vs. 10%), and improved relapse-free survival and OS (although the HR CIs overlapped 1.0). This was achieved with minimal delay in engraftment. This treatment is poised to be the new standard of care in matched sibling transplants following both reduced-intensity conditioning and myeloablative conditioning.

Comment (NC): This ALLG study is practice changing. There was a significant difference in GVHD-free, relapse-free survival between the investigational and standard of care arm. The significant difference indicated the suboptimal GVHD prophylaxis for matched sibling transplants in the last few decades as outcomes for unrelated and haploidentical donor transplants improve. As per the latest EBMT guideline, T-cell depletion is recommended for all sibling matched transplants. It does not answer whether there is any difference between antithymocyte globulin or post-transplant cyclophosphamide. However, the latter is easier to administer and more cost effective. It is becoming the new standard of care for GVHD prophylaxis across different donor types. This is also one of few studies to provide evidence of using the post-transplant cyclophosphamide GVHD prophylaxis platform in myeloablative conditioning regimens in matched donor transplants.

Reference: N Engl J Med 2025;393:243–54
Abstract

Enhanced CAR T-cell therapy for lymphoma after previous failure

Authors: Svoboda J et al.

Summary: Twenty-one patients with relapsed or refractory lymphoma following anti-CD19 CAR T-cell therapy received huCART19-IL18, an anti-CD19 enhanced CAR T-cell product that secretes IL-18. Cytokine-release syndrome occurred in 62% of the participants (47% grade 1–2), and 14% developed ICANS (immune effector-cell-associated neurotoxicity syndrome; all grade 1–2). At 3 months postinfusion, 81% of participants had achieved a CR or PR, with 52% achieving a CR.

Comment (LB): CAR T-cell therapy has revolutionised the treatment of relapsed diffuse large B-cell lymphoma. The current second-generation CAR T-cell products use CD19 externally and CD3ζ internally with a costimulatory CD28 or 4-1BB. However, not everyone responds, and those who relapse have limited options. In addition, the cytokine-release syndrome and more dreaded ICANS can be problematic, and while we have become better at intervening early to manage these reactions, they do complicate treatments. So, can we do better? Enhanced CAR T-cells, nicknamed 'armoured CARs', deliver a cytokine, in this case IL-18, in the hope of improving responses, without causing a dramatic increase in toxicity. This is a proof-of-concept study with most patients having failed prior CAR T-cell therapy. An interesting bonus was the 3-day manufacturing, although 80% still received bridging. The CR rate was an impressive 50%. Albeit with small numbers, there was no dose-response correlation, and levels of IL-18 were not increased due to increased antibody blockade. Next up is presumably a randomised study against conventional CAR T-cells.

Reference: N Engl J Med 2025;392:1824–35
Abstract

Acalabrutinib plus bendamustine-rituximab in untreated mantle cell lymphoma

Authors: Wang M et al., for the ECHO investigators

Summary: Patients aged ≥65 years with previously untreated MCL were randomised to receive acalabrutinib 100mg twice daily (n=299) or placebo (n=299) until disease progression or unacceptable toxicity, along with six cycles of bendamustine 90 mg/m^2 once daily on days 1 and 2 and rituximab 375 mg/m^2 on day 1 followed by maintenance rituximab for 2-year responders; participants were able to crossover to the acalabrutinib arm on disease progression. Compared with placebo, acalabrutinib recipients had a longer median PFS duration (primary endpoint; 66.4 vs. 49.6 months; HR 0.73 [95% CI 0.57, 0.94]), with all subgroups benefitting, including the high-risk feature subgroup. The respective overall response and CR rates were 91.0% and 66.6% in the acalabrutinib arm, and they were 88.0% and 53.5% in the placebo arm. There was no significant between-group difference for OS (p=0.27). The incidences of grade ≥3 adverse events in the respective acalabrutinib and placebo arms were 88.9% and 88.2%.

Comment (LB): BTK (Bruton's tyrosine kinase) inhibitors have high response rates and low toxicity in relapsed/refractory MCL, and this study in older 65-year plus MCL combined acalabrutinib (until progression) with the standard six cycles of rituximab-bendamustine followed by 2 years of maintenance rituximab. Unsurprisingly, this resulted in deeper remissions and better PFS. Whether this is better than sequential treatment with acalabrutinib following rituximab-bendamustine is not yet known. In the acalabrutinib arm, 43% of patients discontinued treatment due to an adverse event (31% discontinued placebo), which is higher than patients on acalabrutinib as monotherapy. Despite 51 of 299 placebo patients crossing over to acalabrutinib, there was a nonsignificant trend for improved survival. The advantage of adding acalabrutinib to rituximab-bendamustine is to delay relapse, but this approach poses problems for the subsequent lines of therapy if acalabrutinib and rituximab-bendamustine are already used. Recent rituximab-bendamustine use is associated with inferior results with CAR T-cells and bispecific antibodies. Chemotherapy-free treatments seem a more desirable option for those MCL patients who are unfit for rituximab-bendamustine-cytarabine therapy.

Reference: J Clin Oncol 2025;43:2276–84
Abstract

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INDEPENDENT COMMENTARY BY
Dr Leanne Berkahn
MB ChB (Otago); FRACP; FRCPA

Leanne Berkahn is a consultant haematologist at Auckland City Hospital and senior lecturer in the Department of Molecular Medicine and Pathology at the University of Auckland School of Medicine. Her current research interests are new therapeutic approaches in the management of leukaemia and lymphoma.

Efficacy of combined CD38 and PD-1 inhibition with isatuximab and cemiplimab for relapsed/refractory NK/T-cell lymphoma

Authors: Kim SJ et al.

Summary: Thirty-seven patients with relapsed or refractory ENKTL received six 4-week cycles of cemiplimab 250mg on days 1 and 15 and isatuximab 10 mg/kg on days 2 and 16, with responders then receiving cemiplimab 350mg and isatuximab 10 mg/kg every 3 weeks for ≤24 months. This regimen was associated with a CR rate (primary endpoint) of 51%, an objective response rate of 65% and a median PFS duration of 9.5 months; median OS duration was not reached. CR was achieved after a median 28 cycles, and among the 24 responders, the median response duration was 29.4 months. Responders exhibited high PD-L1 expression and structural variations that disrupted the 3'-untranslated region of PD-L1. The incidence of grade ≥3 adverse events was 32% and there were no treatment-related deaths.

Comment (LB): Because of the inherent resistance of ENKTL to anthracycline-based chemotherapy, current treatment guidelines recommend alternative strategies, such as non-anthracycline regimens incorporating L-asparaginase, e.g. SMILE regimen (dexamethasone, methotrexate, ifosfamide, pegaspargase, etoposide) and concurrent chemoradiotherapy, for newly diagnosed patients. However, the prognosis for patients with relapsed or refractory ENKTL remains poor following initial treatment, even with salvage therapies and allogeneic SCT. Initial trials with pembrolizumab, a PD-L1 inhibitor, showed efficacy in relapsed or refractory ENKTL, especially in the initial but not real-world trials. The hypothesis in this study was that CD38 blockade could enhance the antitumor activity of PD-1 inhibitors by blocking the downregulation of regulatory T-cells that impacted on an effective T-cell antitumour response. The treatment was especially effective in those with a particular *PD-L1* mutation or with high PD-L1 expression. The median duration of response for responders (24 out of 37 total patients) was 29.4 months (95% CI 15.4, 43.4). The study highlights the benefit of understanding the pathology of the tumour microenvironment and harnessing this knowledge to design more effective therapies.

Reference: Blood 2025;146:155–66
Abstract

Disease risk but not remission status determines transplant outcomes in AML

Authors: Stelljes M et al.

Summary: Long-term outcomes from the ASAP trial were reported; ASAP evenly randomised 281 patients with AML with a poor response to first induction or untreated first relapse to remission induction with high-dose cytarabine plus mitoxantrone or immediate allogeneic SCT with sequential conditioning after nonintensive disease control measures, of which watchful waiting was preferred. There was no significant difference between the disease control measures versus remission induction arms for the 5-year OS rate (46.1% vs. 47.5% [p=0.82]). Study arm assignment was not among the significant predictors of survival on Cox regression analysis, which included genetic risk, age and comorbidities.

Comment (NC): Since the early ASAP trial result was first presented, it has ignited widespread discussion, given it challenges the current dogma in AML treatment. This final analysis confirms the lack of benefit of remission/induction approach to achieve CR prior to allogeneic SCT in those with refractory/relapsed AML. Analysis has shown that biology of the disease dictates outcomes. Patients with adverse disease as per European LeukemiaNet classification, or poor response to induction in the remission induction arm or requiring low-dose chemotherapy to control disease prior to transplant in the nonintensive disease control measures arm had the worst outcomes. This study result may lead to changes in approach to AML treatment in the early relapse setting. It also shows the need for a different approach to high-risk disease, especially in patients with *tp53* mutation.

Reference: Blood; Online July 30, 2025
Abstract

From CyBorD to dara-CyBorD, ASCT utilization trends in AL amyloidosis

Authors: Muchtar E et al.

Summary: These researchers reported on two retrospective US cohorts of 441 patients with AL (light-chain) amyloidosis attending the Mayo Clinic; cohort one covered the 2010–2019 period and cohort 2 covered the 2020–2024 period. Compared with cohort 1, cohort 2 showed a significant 71% annual decrease in autologous SCTs, and the patients were older and were more likely to have relapsed or refractory disease. Cohort 2 also had a higher baseline bone marrow plasma cell burden compared with cohort 1, their pretransplant induction use was more frequent (89.3% vs. 56.4%), with the predominant induction regimen being the addition of daratumumab to CyBorD (cyclophosphamide-bortezomib-dexamethasone), although lymphoma-based regimens were also more common (15.1% vs. 5.3% [p=0.02]), and their 10-day satisfactory haematological response rate was higher (91.1% vs. 72.7% [p=0.001]), but their haematological CR rate did not differ significantly (50.9% vs. 38.8% [p=0.09]).

Comment (NC): This paper nicely outlines the progress with treatment of AL amyloidosis over the last 15 years. Certainly with the use of more effective induction regimens, the utilisation of autologous SCT has reduced. While this is not based on a randomised study, the key to longer-term outcomes is by achieving haematological response. If this is attainable with induction, then autologous SCT is often delayed until relapse, given the significant morbidity and mortality associated with transplantation in this group. The majority of centres around the world are following a similar practice for autologous SCT in AL amyloidosis.

Reference: Blood Adv 2025;9:4311–6
Abstract

Venetoclax or placebo in combination with bortezomib and dexamethasone in relapsed or refractory multiple myeloma (BELLINI)

Authors: Kumar SK et al.

Summary: Final survival results were reported for the phase 3 BELLINI trial, which randomised adults with relapsed or refractory MM to receive eight 21-day cycles of oral venetoclax 800mg (n=194) or placebo (n=97) once daily added to bortezomib 1.3 mg/m^2 and dexamethasone 20mg, followed by 35-day cycles until discontinuation; 28 and five participants from the respective arms were still on treatment at the time of this analysis. After a median 45.6 months of follow-up, there was no significant difference between the venetoclax and placebo groups for median OS duration (not reached in both arms [p=0.39]), but median investigator-assessed PFS duration was longer in the venetoclax arm (23.4 vs. 11.4 months [p=0.00026]). The most common grade 3–4 adverse events were thrombocytopenia (26% and 40% in the venetoclax and placebo groups, respectively) and neutropenia (30% and 8%). There were four fatal treatment-related adverse events in the venetoclax arm but none in the placebo arm.

Comment (LB): This study is a textbook case of how a promising drug can be destroyed by poor trial design. Going into the study, there was strong data for the beneficial effect of Bcl-2 inhibition by venetoclax in t(11;14) myeloma, and lack of evidence in other MM. The results showed better responses translating to better OS in the t(11;14) subset, but this was swamped by excess deaths due to toxicity in the others. There was no specific toxicity identified, but there were more infectious deaths in nonresponders. While the dose of 600mg of venetoclax may be too high, or the bortezomib and dexamethasone may not be the ideal partner, the main reason this study failed is because the inclusion criteria included allcomers, and poor results in higher risk patients overshadowed the success in the t(11;14) group.

Reference: Lancet Haematol 2025;12:e574–87
Abstract

Belantamab mafodotin plus bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (DREAMM-7)

Authors: Hungria V et al., on behalf of the DREAMM-7 study investigators

Summary: This was an updated OS analysis after a median 39.4 months of follow-up for the open-label phase 3 DREAMM-7 trial, which randomised adults with MM to receive 21-day cycles of subcutaneous bortezomib 1.3 mg/m^2 twice weekly and dexamethasone 20mg with either intravenous belantamab mafodotin 2.5 mg/kg (BVd; n=243) or intravenous daratumumab 16 mg/kg (DVd; n=251). Although median OS duration was not reached in either arm, the statistical analysis showed it was significantly longer in the BVd arm than in the DVd arm (p=0.0002), with BVd recipients having a higher MRD-negativity rate with a CR or better (25% vs. 10%), a longer median duration of response (40.8 vs. 17.8 months), and a longer median PFS2 duration following subsequent antimyeloma therapy (not reached vs. 33.4 months; HR 0.59 [95% CI 0.45, 0.77]). Regarding adverse events: i) the most frequent of grade 3 or 4 was thrombocytopenia (56% and 35% with BVd and DVd, respectively); ii) the serious adverse event incidences in the respective BVd and DVd arms were 53% and 38%, the most frequent of which were pneumonia (12% and 4%), pyrexia (5% and 4%) and COVID-19 (5% and 4%); and iii) there were seven fatal treatment-related adverse events in the BVd arm and two in the DVd arm.

Comment (NC): This is an updated result of the DREAMM-7 trial, which previously showed a PFS benefit of BVd versus DVd. The updated results confirmed the significant OS benefit of BVd, including in those with high-risk cytogenetic abnormalities. There was a high frequency (around 90%) of ocular toxicity noted across DREAMM-7 and DREAMM-8, necessitating dose modification without impacting outcomes (Mateos et al. Blood Adv; Online Aug 5, 2025). The need for regular ophthalmic examination can be challenging in routine practice. Belantamab mafodotin is seeking approval in various jurisdictions based on the results of the DREAMM7 and DREAMM8 studies.

Reference: Lancet Oncol 2025;26:1067–80
Abstract

Isatuximab, carfilzomib, lenalidomide, and dexamethasone induction in newly diagnosed myeloma

Authors: Perrot A et al.

Summary: The phase 3 MIDAS study in 791 patients with newly diagnosed MM is evaluating a strategy of MRD-driven consolidation and maintenance after induction with six 28-day cycles of isatuximab-carfilzomib-lenalidomide-dexamethasone, which was completed by 757 participants. With a median CD34+ cell yield of 7×10^6/kg, 94% of participants were able to proceed to a potential tandem transplant. The best overall response rate was 95%. The VGPR or better rate after induction in the intent-to-treat population was 91%, with MRD negativity rates of 63% and 47% at 10^{-5} and 10^{-6}, respectively. Disease progression occurred in seven participants during induction, with one death as a result; there were also two deaths from cardiac events and two from other causes. Neutropenia (25%), thrombocytopenia (5%) and infections (7%) were the most frequently recorded grade 3–4 adverse events. Any-grade peripheral neuropathy occurred in 13% of participants.

Comment (NC): This study design is ambitious and aims at using MRD result after induction to determine the intensity of subsequent therapy. Patients with MRD-negative disease are randomised to upfront autologous SCT versus further cycles of isatuximab-carfilzomib-lenalidomide-dexamethasone, and those with MRD-positive disease are randomised to single versus tandem transplantation. This is different to the current established antimyeloma therapy where treatment is dictated mainly by baseline prognostic results. The early results show this approach is safe and feasible, which is not surprising, as a similar combination has been previously used in this patient group. More importantly, it has a reasonably high rate of achieving MRD-negative disease after six cycles of induction. Longer-term results will be interesting and may be practice changing.

Reference: Blood 2025;146:52–61
Abstract

INDEPENDENT COMMENTARY BY

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