Lymphoma & Leukaemia Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

ALL = acute lymphoblastic leukaemia
alloHSCT = allogeneic haematopoietic stem cell transplantation
AML = acute myeloid leukaemia
APL = acute promyelocytic leukaemia
ASCT = autologous stem cell transplantation
CAR = chimeric antigen receptor
CLL = chronic lymphocytic leukaemia
DLBCL = diffuse large B-cell lymphoma
GVHD = graft-versus-host-disease
HL = Hodgkin lymphoma
MDS = myelodysplastic syndrome
MRD = minimal residual disease
NHL = non-Hodgkin lymphoma
R/R = relapsed/refractory

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Welcome to issue 29 of Lymphoma and Leukaemia Research Review.

A phase I/II study from the *Journal of Clinical Oncology* has established the feasibility, safety, and efficacy of an ex vivo expanded umbilical cord blood unit as a stand-alone graft. A well-designed study published in *Lancet Oncology* provides strong evidence that a PET-adapted de-escalated approach for PET2-negative advanced Hodgkin lymphoma patients is non-inferior to 6x $BEACOPP_{escalated}$ but associated with less toxicity. Researchers from Japan have reported on a series of five patients with haematological malignancies who underwent salvage cord blood transplantation using a conditioning regimen of fludarabine, melphalan and low-dose antithymocyte globulin after primary graft failure following allogeneic SCT.

We hope you find the selection for this month's edition useful in your practice, and we look forward to receiving your comments or feedback.

Kind Regards

Professor Maher Gandhi

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Nivolumab for relapsed/refractory diffuse large B-cell lymphoma in patients ineligible for or having failed autologous transplantation

Authors: Ansell SM et al.

Summary: In this phase II study, patients with R/R DLBCL who were ineligible for or who had failed ASCT, received nivolumab every 2 weeks. At a median follow-up of 9 months in the failed cohort (n=87) and 6 months in the ineligible cohort (n=34), objective response rates were 10% and 3%, and median durations of response were 11 and 8 months, respectively. Median PFS was 1.9 months in the failed cohort and 1.4 months in the ineligible cohort and median overall survival was 12.2 months and 5.8 months, respectively. Complete remission was achieved by three patients in the failed cohort and all three had a durable response (11 to 17 months). The most common treatment-related grade 3 and 4 adverse events were neutropenia (4%), thrombocytopenia (3%), and increased lipase (3%). 9p24.1 analysis showed that 16% of evaluable samples had low-level copy gain and 3% had amplification.

Comment: Results are disappointing and it was interesting that in the three responders only one had PD-L1/L2 copy number gain, indicating the biological basis for response (or lack of it) remains unclear. It would have been interesting if investigators had tested for B2M status and other measures of intact antigen presentation, and also mutational tumour burden. Also, perhaps the tolerability of anti-PD-1, indicates combination strategies (e.g. to prolong CAR T cell survival) may be worthwhile exploring.

Reference: J Clin Oncol. 2019;37(6):481-489.

Abstract

Lymphoma and Leukaemia Research Review™

Independent commentary by Maher Gandhi
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Professor Gandhi undertook his specialist training in Cambridge and Toronto and completed a PhD in immunology in Cambridge. He is the Director of Clinical Research at the Mater Research Institute, University of Queensland, runs the Blood Cancer Research Group, and is a Senior Staff Haematologist at the Princess Alexandra Hospital in Brisbane. He is a member of a number of Australian and international professional societies, committees and editorial boards, and has published several books and numerous blood cancer research papers.

Phase I/II study of stem-cell transplantation using a single cord blood unit expanded ex vivo with nicotinamide

Authors: Horwitz ME et al.

Summary: This study evaluated the safety and efficacy of an umbilical cord blood (UCB) graft that was expanded ex vivo with nicotinamide among 36 patients with haematologic malignancies. At day 42, the incidence of neutrophil engraftment was 94%. Haematopoietic recovery was compared to that of 146 patients undergoing standard UCB transplantation. The median time to neutrophil recovery was 11.5 days in the nicotinamide group and 21 days in the standard group (P<0.001) and median time to platelet recovery was 34 days and 46 days, respectively (P<0.001). At day 100, the incidence of grade 3-4 acute GVHD was 11% and at 2 years the incidence of all chronic GVHD was 40%, and moderate/severe chronic GVHD was 10%. At 2 years, the incidences of non-relapse mortality and relapse were 24% and 33%, respectively, and the probabilities of overall and disease-free survival were 51% and 43%, respectively.

Comment: CB transplant has the major advantage of reduced GVHD, but its drawback is the slow engraftment – even for patients receiving double CB transplant. In this study, single CB units were immunomagnetically sorted into T-cell depleted and T-cell components. The former were expanded in vitro for 3 weeks (with FLT3Ligand, SCF, TPO, IL-6, nicotinamide analogue: which increases the number of phenotypically primitive CD34+CD38- cells) whilst the T-cell component was unmanipulated and cryopreserved. Re-infusion (of the expanded component and the T-cells combined) resulted in faster engraftment and had an acceptable safety profile.

Reference: J Clin Oncol. 2019;37(5):367-374.
Abstract

Fixed duration of venetoclax-rituximab in relapsed/refractory chronic lymphocytic leukemia eradicates minimal residual disease and prolongs survival

Authors: Kater AP et al.

Summary: This report is a post-treatment follow-up of the phase III MURANO study which showed a significant PFS benefit for fixed-duration venetoclax-rituximab (VR) compared with bendamustine-rituximab (BR) in R/R CLL. Among 194 patients, 174 completed the VR phase and 130 completed 2 years of venetoclax. At a median follow-up of 36 months, PFS and OS remained superior to BR (HR, 0.16; 95% CI, 0.12 to 0.23; and HR, 0.50; 95% CI, 0.30 to 0.85, respectively). At the end of combination therapy, the VR group had a higher rate of undetectable MRD (62% vs 13%) with superiority maintained through month 24. Undetectable MRD status predicted longer PFS. After completion of VR therapy (median 9.9 months) 12% of patients had disease progression. At the end of therapy, 70% of patients with undetectable MRD remained undetectable and 98% of patients with undetectable MRD remained without disease progression.

Comment: MURANO was a landmark international study for R/R CLL, showing superior PFS and rates of undetectable MRD in VR versus BR treated patients. The new manuscript provides updated data now that all patients have completed maintenance venetoclax (achieved in two-thirds), showing that PFS is sustained with low conversion to detectable MRD.

Reference: J Clin Oncol. 2019;37(4):269-277.
Abstract

Double-hit gene expression signature defines a distinct subgroup of germinal center B-cell-like diffuse large B-cell lymphoma

Authors: Ennishi D et al.

Summary: By analysing RNA sequencing data from 157 *de novo* GCB (germinal centre B-cell-like)-DLBCLs, including 25 high-grade B-cell lymphomas with *BCL2* rearrangements, these researchers defined a gene expression signature that was able to distinguish the grade B-cell lymphomas with *BCL2* rearrangement from other GCB-DLBCLs. The 104-gene double-hit signature, DHITsig, assigned 27% of GCB-DLBCLs to the DHITsig-positive group, with only half of them harbouring *MYC* and *BCL2* rearrangements. Patients from this DHITsig-positive group had worse outcomes than DHITsig-negative patients after R-CHOP, with a lower 5-year time to progression rate (57% vs 81%; P < 0.001), irrespective of high-grade B-cell lymphomas with *BCL2* rearrangement status. The prognostic value of DHITsig was confirmed in an independent validation cohort. The researchers were able to translate these findings into an assay that could be applied to routinely available biopsy samples, enabling further investigation of its utility for guiding patient management.

Comment: This represented one of two papers in the same edition (the other was from Leeds using a Burkitt-like signature) describing novel molecular signatures for double-hit lymphomas. This new DHIT signature sub-group of GCB-DLBCL roughly doubles the number of high-grade B-cell lymphomas that would be classified by FISH testing. This is unsurprising: MYC upregulation can arise from many processes beyond just translocation. There is partial overlap with the EZB genetic subgroup identified by Schmitz (*NEJM* 2017), suggesting that each category does not adequately capture the other. Interestingly, the DHIT signature was associated with reduced immune/inflammation markers and loss of MHCI/II expression was more frequent, all indicating impaired immune surveillance. The best strategies to manage DHIT signature positive patients will need addressing in prospective trials.

Reference: J Clin Oncol 2019;37:190–201
Abstract

PET-adapted treatment for newly diagnosed advanced Hodgkin lymphoma (AHL2011)

Authors: Casasnovas R-O et al.

Summary: In this study, 823 patients with newly-diagnosed HL received two cycles of $BEACOPP_{escalated}$, after which PET assessment was done (PET2). Patients were then randomised to receive standard treatment (two further cycles of $BEACOPP_{escalated}$ induction therapy irrespective of PET2 results) or PET-driven treatment (two additional cycles of $BEACOPP_{escalated}$ in PET2-positive patients or switch to two cycles of ABVD in PET2-negative patients). In both groups, PET results determined whether to continue with consolidation in those with negative scans or start salvage therapy in those with positive scans. At median follow-up of 50.4 months, 5-year PFS by ITT was 86.2% in the standard group and 85.7% in the PET-driven group (P=0.65). The most common grade 3-4 adverse events were leucopenia (92% in the standard group vs 95% in the PET-driven group), neutropenia (87% vs 90%), anaemia (69% vs 28%), thrombocytopenia (66% vs 40%), febrile neutropenia (35% vs 23%), and infections (22% vs 11%). Serious treatment-related adverse events occurred in 47% of patients in the standard group and 28% of patients in the PET-driven group, including infections (20% vs 12%) and febrile neutropenia (5% vs 6%). Six patients in the standard treatment group had fatal treatment-related events (septic shock [n=2], pneumopathy [n=2], heart failure [n=1], AML [n=1]), as did two in the PET-driven group (septic shock and AML [n=1 each]).

Comment: $BEACOPP_{escalated}$ improves PFS but is associated with increased risks of haematological toxicity, secondary MDS/leukaemia, and infertility. This well-designed study provides strong evidence that a PET-adapted de-escalated approach for PET2-negative advanced HL patients is non-inferior to 6x $BEACOPP_{escalated}$ but associated with less toxicity. The inclusion of adolescents (frequently excluded from HL RCTs) was commendable.

Reference: Lancet Oncol. 2019;20(2):202-215.
Abstract

Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1)

Authors: Locke FL et al.

Summary: This analysis reported long-term outcomes of the ZUMA-1 study, in which patients with refractory large B-cell lymphoma received axicabtagene ciloleucel, an autologous anti-CD19 CAR T-cell therapy. Patients received one dose of axicabtagene ciloleucel after conditioning chemotherapy with fludarabine and cyclophosphamide. Among 101 evaluable patients (median follow-up 27.1 months), the objective response rate was 83%, the complete response rate was 58%, the median duration of response was 11.1 months, the median overall survival was not reached, and the median PFS was 5.9 months. Among 108 patients evaluable for safety, grade ≥3 serious adverse events occurred in 48% of patients, including neurological events (32%) and cytokine release syndrome (11%). Subsequent to the previous analysis at 1 year, additional grade ≥3 serious adverse events were observed in four patients (mental status changes, MDS, lung infection, and bacteraemia), none of which were treatment related. No new treatment-related deaths occurred during the additional follow-up.

Comment: Response rates (including CRs) are exceptional for this group of patients. In this long-term follow-up (it extends this by 1 year to a reasonable median 27 months) the safety profile remains unchanged. However, the almost one year duration of response (although not reached for complete responders with the emergence of a plateau curve) and 6 months PFS remains a concern, suggesting that CAR T cells should either be a bridge to something else, or be used as part of a combination strategy, particularly in patients that fail to reach CR. Newer generation CARs may also provide the answer.

Reference: Lancet Oncol. 2019;20(1):31-42.
Abstract

Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE)

Authors: Moreno C et al.

Summary: In this, open-label, phase III trial 229 patients with previously untreated CLL or small lymphocytic lymphoma (≥65 years or <65 years with coexisting conditions) were randomised to receive ibrutinib plus obinutuzumab or chlorambucil plus obinutuzumab. At a median follow-up of 31.3 months, median PFS was not reached in the ibrutinib plus obinutuzumab group versus 19.0 months in the chlorambucil plus obinutuzumab group (P<0.0001). Estimated 30-month PFS was 79% versus 31%, respectively. The most common grade 3 or 4 adverse events overall were neutropenia and thrombocytopenia. Serious adverse events were reported in 58% of the ibrutinib plus obinutuzumab group and 35% of the chlorambucil plus obinutuzumab group, while treatment-related deaths were reported in one (sudden death) and one (neuroendocrine carcinoma of the skin) patient, respectively.

Comment: The study met its primary endpoint, i.e. in a (fairly healthy) elderly CLL population, continuous treatment with ibrutinib plus obinutuzumab, is more efficacious (longer PFS) than 6 months of chlorambucil and obinutuzumab, including patients with high-risk disease features. Any interesting question that remains to be addressed is whether second generation anti-CD20 mAbs potentiate ibrutinib (a recent phase RCT suggests rituximab does not). Teasingly, the proportion of patients achieving undetectable MRD was higher than prior reports with ibrutinib monotherapy.

Reference: Lancet Oncol. 2019;20(1):43-56.
Abstract

Safety and activity of ibrutinib in combination with nivolumab in patients with relapsed non-Hodgkin lymphoma or chronic lymphocytic leukaemia

Authors: Younes A et al.

Summary: This study evaluated the safety and efficacy of ibrutinib plus nivolumab in patients with R/R B-cell malignancies. Among 141 evaluable patients, the most common grade 3-4 adverse events were neutropenia (28%) and anaemia (23%), the most common serious adverse events were anaemia (4%) and pneumonia (4%), and the most common grade 3-4 immune-related adverse events were rash (8%) and increased alanine aminotransferase (2%). The overall response rate was 65% among patients with Richter's transformation, 61% among patients with high-risk CLL or small lymphocytic lymphoma, 36% among patients with DLBCL, and 33% among patients with follicular lymphoma.

Comment: Although adding nivolumab to ibrutinib had a safety profile that was consistent with the known profile of each agent alone, there was no added clinical benefit to the combination. The exception was Richter's transformed patients, in which expression of the PD-1 ligand (PD-L1) has been shown to be increased in Richter's transformation compared with *de-novo* DLBCL, an area of unmet need in which responses to chemoimmunotherapy are typically short-lived.

Reference: Lancet Haematol. 2019;6(2):e67-e78
Abstract

GVHD prophylaxis plus ATLG after myeloablative allogeneic haemopoietic peripheral blood stem-cell transplantation from HLA-identical siblings in patients with acute leukaemia in remission

Authors: Bonifazi F et al.

Summary: Patients with AML and ALL in remission, having alloHSCT with peripheral blood stem cells from an HLA-identical sibling donor after myeloablative conditioning, were randomised to receive anti-T-lymphocyte globulin (ATLG) plus standard GVHD prophylaxis (ATLG group) or standard GVHD prophylaxis without ATLG (non-ATLG group). The primary and secondary endpoints, excluding QoL, have been previously published. A follow-up extension including 114 patients was performed. Global health status had a more favourable time course in the ATLG group compared to the non-ATLG group (P=0.02). ATLG was superior to non-ATLG at 24 months for physical function (P=0.014), social function (P=0.047), gastrointestinal adverse events (P=0.008) and effect on family (P=0.032). With a median follow-up of 5.9 years, the ATLG group had a significant benefit compared to the non-ATLG group with respect to 5-year chronic GVHD (cGVHD) incidence (30.0% vs 69.1%; P<0.001), no increase in relapses (35.4% vs 22.5%; P=0.09), improved cGVHD-free, relapse-free survival (34.3% vs 13.9%; P=0.005), and patients in immunosuppression (9.6% vs 28.3%; P=0.017).

Comment: This follow-up report of the primary (*NEJM* 2016) manuscript provides follow-up on the small sub-group of survivors in both the ATLG and non-ATLG arms. Data supports the addition of ATLG in vivo T-cell depletion in terms of cGHVD (findings replicated in other trials). However, the observation that relapse and PFS is improved is not consistent with other studies (some of which find no difference, others find higher relapse). Explanations include patient selection and small sample size.

Reference: Lancet Haematol. 2019;6(2):e89-e99.
Abstract

Tamibarotene maintenance improved relapse-free survival of acute promyelocytic leukemia

Authors: Takeshita A et al.

Summary: The final results were reported for the prospective JALSG-APL204 trial, which compared tamibarotene with all-*trans* retinoic acid as maintenance therapy for newly diagnosed APL; median follow-up was 7.3 years. Among 344 eligible all-*trans* retinoic acid plus chemotherapy recipients, the complete remission rate was 93%. After completing three courses of consolidation chemotherapy, 269 patients in molecular remission were randomised to 2 years of maintenance therapy with all-*trans* retinoic acid 45 mg/m^2/day (n=135) or tamibarotene 6 mg/m^2/day (n=134) for 14 days every 3 months. Compared with the all-*trans* retinoic acid arm, the tamibarotene arm has a significantly greater 7-year RFS rate (primary endpoint; 93% vs 84%; HR 0.44; 95% CI 0.21–0.93), especially for high-risk participants with an initial leucocyte count of ≥10.0 × 10^9/L (89% vs 62%; P=0.034). There was no significant between-group difference for post-randomisation OS. Nine participants developed secondary haematopoietic disorders, 11 developed secondary malignancies, and three experienced grade ≥3 late cardiac comorbidities; there were no differences between the two study arms for these late complications

Comment: Tamibarotene is a new synthetic retinoid that is more potent to ATRA in inducing in vitro differentiation, that is believed to induce less resistance and have more favourable pharmacokinetics. This study achieved its primary endpoint, showing superior 7-year RFS (survival was similar) with tamibarotene maintenance, which was most prominent in those with high-risk disease. Incidence of late complications was similar.

Reference: Leukemia 2019;33:358–70
Abstract

