Lymphoma & Leukaemia Research Review™

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Issue 31 - 2019

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Abbreviations used in this issue:

AML = acute myeloid leukaemia
ASCT = autologous stem cell transplantation
CLL = chronic lymphocytic leukaemia
DLBCL = diffuse large B-cell lymphoma
DOR = duration of response
EFS = event-free survival
MCL = mantle cell lymphoma
MDS = myelodysplastic syndrome
MRD = minimal residual disease
NGS = next generation sequencing
NHL = non-Hodgkin lymphoma
R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
R-CVP = rituximab, cyclophosphamide, vincristine, prednisone
TKI = tyrosine kinase inhibitor

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Welcome to issue 31 of Lymphoma and Leukaemia Research Review.

We begin this issue with a study showing that venetoclax plus low-dose cytarabine has a manageable safety profile, producing rapid and durable remissions in older adults with AML ineligible for intensive chemotherapy. Other research reports that bendamustine plus rituximab had better long-term disease control than R-CHOP/R-CVP in patients with indolent and mantle-cell lymphoma and should be considered as a first-line treatment option. In Hodgkin lymphoma, second-line brentuximab vedotin plus etoposide, solumedrol, high-dose cytarabine, and cisplatin appears to be a safe and effective pre-transplant induction regimen, does not jeopardize transplant and permits long-term remissions and survival.

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

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Venetoclax combined with low-dose cytarabine for previously untreated patients with acute myeloid leukemia

Authors: Wei AH, et al.

Summary: This phase Ib/II study evaluated venetoclax plus low-dose cytarabine (LDAC) in 82 elderly patients (mean age 74 years) with previously untreated AML who were ineligible for intensive chemotherapy. Patients received oral venetoclax 600 mg/day in 28-day cycles, plus LDAC (20 mg/m^2/day) on days 1 to 10. Forty-nine percent of patients had secondary AML, 29% had previous hypomethylating agents (HMAs) for MDS, and 32% had poor-risk cytogenetics. Common grade ≥3 AEs were febrile neutropenia (42%), thrombocytopenia (38%), and decreased WBC count (34%). Thirty-day mortality was 6%. CR/CR with incomplete blood count recovery was 54% (median time to first response, 1.4 months), median OS was 10.1 months, and median DOR was 8.1 months. Among patients without previous HMA treatment, CR/CR with incomplete blood count recovery was 62%, median OS was 13.5 months, and median DOR was 14.8 months.

Comment: The outlook for elderly AML (the median age is 68) is grim, and therapies such as LDAC are frequently given with palliative intent. However, new developments will likely see new 'standards of care' emerge. A phase II study reported an ORR of 19% with venetoclax monotherapy in heavily pretreated patients with AML. The agent has also been successfully used in combination with other therapeutics (including HMAs) in a variety of malignancies. In this highly encouraging study led by Monash's Andrew Wei, venetoclax plus LDAC produced rapid remissions in older adults with AML ineligible for intensive chemotherapy with a manageable safety profile. Combination with other agents (such as HMAs) should be explored as a way to improve durability of response and survival.

Reference: J Clin Oncol. 2019;37(15):1277-1284.
Abstract

Randomized phase III trial of ibrutinib and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in non–germinal center B-cell diffuse large B-cell lymphoma

Authors: Younes A, et al.

Summary: In this double-blind phase III study 838 patients (median age 62 years) with untreated non-germinal centre B-cell (GCB) DLBCL were randomised to receive ibrutinib plus R-CHOP or placebo plus R-CHOP. Three quarters of evaluable patients (75.9%) had activated B-cell (ABC) disease. Ibrutinib plus R-CHOP did not improve EFS (primary endpoint) in the ITT (HR 0.934) or ABC (HR 0.949) population. However, in younger patients (<60 years), ibrutinib plus R-CHOP improved EFS (HR 0.579), PFS (HR 0.556), and OS (HR 0.330) and increased serious AEs (35.7% vs 28.6% for placebo plus R-CHOP), but the number of patients able to receive at least six cycles of R-CHOP was similar between groups (92.9% vs 93.0%). In older patients (≥60 years), ibrutinib plus R-CHOP was associated with increased serious AEs (63.4% vs 38.2% for placebo plus R-CHOP), leading to a decreased proportion of patients receiving at least six cycles of R-CHOP (73.7% vs 88.8%) and worsened EFS, PFS, and OS.

Comment: Despite improved insights into its biology, and multiple attempts to improve outcomes, including early ASCT, addition of bortezomib or lenalidomide and alternate chemoimmunotherapy backbones such as R-EPOCH, nothing has been shown to be definitively better than R-CHOP for front-line DLBCL. This study attempted to utilise ibrutinib's known ability to suppress lymphoma cell NFKB-driven proliferation, by combining it upfront with R-CHOP. Although the team are to be commended for successfully completing such a large trial, questions remain about the appropriateness of the study design, including use of the Hans classifier to enrich for non-GCB, delay in commencement of therapy (which might result in potential selection bias for favourable patients) and over-emphasis on post-hoc analysis. Importantly, the study did not meet its primary end point in the ITT or ABC population. A phase III trial adding ibrutinib during and after high-dose chemotherapy and ASCT in patients with recurrent non-GCB DLBCL is ongoing.

Reference: J Clin Oncol. 2019;37(15):1285-1295.
Abstract

First-line treatment of patients with indolent non-Hodgkin lymphoma or mantle-cell lymphoma with bendamustine plus rituximab versus R-CHOP or R-CVP

Authors: Flinn IW, et al.

Summary: Five-year follow-up data were reported from the BRIGHT study, which compared bendamustine plus rituximab with R-CHOP or R-CVP in treatment-naive patients with indolent NHL or MCL. Medians were not reached with any of the treatments for investigator-assessed PFS, EFS, DOR or OS. Compared with R-CHOP/R-CVP, bendamustine plus rituximab was associated with a higher 5-year PFS rate (65.5% vs 55.8%; P=0.0025) and significantly greater EFS and DOR, but OS did not differ significantly. Bendamustine plus rituximab was associated with greater development of secondary malignancies.

Comment: The data suggest that bendamustine plus rituximab provides greater disease control than R-CHOP/R-CVP for indolent NHL. However, the absence of a significant improvement in OS in both the BRIGHT and StiL studies suggests that the sequence of these therapies is not of major consequence. The greater incidence in secondary malignancies seen with bendamustine plus rituximab was mainly accounted for by SCCs and BCCs is interesting and may be a consequence of heightened immune depletion, although this was not observed in StiL.

Reference: J Clin Oncol. 2019;37(12):984-991.
Abstract

Brentuximab vedotin and ESHAP is highly effective as second-line therapy for Hodgkin lymphoma patients

Authors: Garcia-Sanz R, et al.

Summary: This trial by the Spanish GELTAMO Group evaluated brentuximab vedotin plus etoposide, solumedrol, high-dose cytarabine, and cisplatin (BRESHAP) as second-line therapy for R/R Hodgkin lymphoma. Responding patients received ASCT, followed by three cycles of brentuximab vedotin. Among 66 patients (median age 36 years) 40 were primary refractory, 16 had early relapse and 10 had late relapse. Thirty-nine reports of severe AEs occurred in 22 patients, including 25 incidents of fever (35% neutropenic) and 3 deaths. Grade 3-4 haematological AEs were neutropenia (n=21), thrombocytopenia (n=14), and anaemia (n=7), while grade ≥3-4 nonhaematological AEs were non-neutropenic fever (n=13) and hypomagnesaemia (n=3). ORR before transplant was 91%, including 70% CR. Sixty patients were successfully transplanted, for a CR of 82% and PR of 10%. After a mean follow-up of 27 months, the 30-month time to treatment to failure was 74%, PFS 71%, and OS 91%.

Comment: High-dose chemotherapy with ASCT is the gold-standard for R/R classic Hodgkin lymphoma. In almost all studies, the strongest predictor of outcome is disease status after re-induction therapy. Therefore, the choice of a highly active pre-transplant salvage regimen that combines stem-cell mobilizing potential, low-toxicity and efficacy is critical. The only different effect compared to ESHAP was an increase in grade 3–4 neutropenia, although this did not translate into a higher rate of febrile neutropenia. Peripheral neuropathy was not a major problem. BRESHAP looks to be a safe and effective pre-transplant induction regimen.

Reference: Ann Oncol. 2019;30(4):612-620.
Abstract

Lenalidomide in combination with intravenous rituximab (REVRI) in relapsed/refractory primary CNS lymphoma or primary intraocular lymphoma

Authors: Ghesquieres H, et al.

Summary: This phase II study of the French Oculo-Cerebral lymphoma Network and the Lymphoma Study Association evaluated rituximab plus lenalidomide (R^2) in R/R DLBCL-primary central nervous system lymphoma (PCNSL) or primary vitreoretinal lymphoma (PVRL). ORR at the end of induction was 35.6% among 45 evaluable patients and 32.0% in the ITT analysis, including 13 CR/unconfirmed CRs (29%) and 3 PRs (7%). At median follow-up of 19.2 months, the median PFS was 7.8 months and median OS was 17.7 months. Median PFS was 9.5 months for patients with a peripheral baseline CD4/CD8 ratio of ≥1.6 compared to 2.8 months for those with a CD4/CD8 ratio of <1.6 (P=0.03). No unexpected AEs were noted.

Comment: This phase II 'proof-of-concept' study met its primary end point and proved that the R^2 regimen has activity against R/R lymphoma within both the intracranial and ocular compartments, although given the results of NHL24 how much rituximab adds to lenalidomide (the latter is known to penetrate the CSF and has single-agent activity) is questionable. Maximal response was during the first 4 months, and unlike a prior study which suggested potential benefit of maintenance lenalidomide, there was little benefit to maintenance here. The study concludes by claiming the study supports testing R^2 in combination with methotrexate-based therapy, which is understandable, but hopefully the future will hold combinations with less toxic and more targeted agents than methotrexate, such as BTK-inhibitors.

Reference: Ann Oncol. 2019;30(4):621-628.
Abstract

Polatuzumab vedotin or pinatuzumab vedotin plus rituximab in patients with relapsed or refractory non-Hodgkin lymphoma

Authors: Morschhauser F, et al.

Summary: This phase II randomised study (ROMULUS) compared rituximab plus the antibody-drug conjugate (ADC) polatuzumab vedotin (R-pola) or rituximab plus the ADC pinatuzumab (R-pina) in patients with R/R DLBCL (n=81) or follicular lymphoma (n=42). In the DLBCL group, grade 3-5 AEs occurred in 79% of patients receiving R-pina, including neutropenia (29%), hyperglycaemia (10%) and grade 5 AEs (21%; five of which were infection-related), and in 77% of patients receiving R-pola, including neutropenia (23%), anaemia (8%), and diarrhoea (8%); no grade 5 AEs. In the follicular lymphoma group, grade 3-5 AEs occurred in 62% of patients receiving R-pina, including neutropenia (29%) and hyperglycaemia (14%) (no grade 5 AEs), and in 50% of patients receiving R-pola, including neutropenia (15%) and diarrhoea (10%); one grade 5 AE. In the DLBCL cohort, objective response was achieved by 60% of the R-pina group and 54% of the R-pola group and complete response was achieved by 26% and 21%, respectively. In the follicular lymphoma cohort, objective response was achieved by 62% of the R-pina group and 70% of the R-pola group and complete response was achieved by 5% and 45%, respectively.

Comment: Included in this phase IIb study were heavily pretreated patients, the majority refractory to the last treatment, thus the responses are promising, with a duration of response of just over 1 year in DLBCL and 9 months in follicular lymphoma. Although the safety profile of polatuzumab is manageable, peripheral neuropathy may be a matter of concern. Hopefully the future of ADCs in combination with chemotherapy will hold up to scrutiny in larger trials.

Reference: Lancet Haematol. 2019;6(5):e254-e265.
Abstract

Effect of low-level *BCR-ABL1* kinase domain mutations identified by next-generation sequencing in patients with chronic myeloid leukaemia

Authors: Kizilors A, et al.

Summary: Ninety-nine consecutive patients with newly diagnosed CML treated with first-line TKIs, and 22 patients identified at the time of resistance to first-line treatment with imatinib, were screened for *BCR-ABL1* kinase domain mutations with NGS in this population-based study. When a mutation was detected, all previous samples were also screened to determine when the mutant subclone(s) first emerged and the subsequent kinetics. The first-line TKI was imatinib for 111 patients, nilotinib for seven and dasatinib for three. Kinase domain mutations were detected in 21% of the patients, among whom low-level kinase domain mutations were first detected in 68%. Among screened patients who achieved a complete cytogenetic response (n=93), 14% had a mutation. Loss of complete cytogenetic response was significantly more frequent among patients with a clinically relevant mutation than in those without (71% vs 17%; P=0.0031). Compared with patients with no mutation, those with a mutant clone had lower 5-year PFS and EFS rates (65.3% vs 86.9%; P=0.0161 and 22.2% vs 62.0%; P<0.0001, respectively). Among patients with samples available at 3 months after starting first-line TKI treatment, 10% had a kinase domain mutation detected, all of whom progressed to accelerated phase disease versus only 8% of patients without a mutation (P<0.0001).

Comment: Mutations at key sites in the *BCR-ABL1* kinase domain can abrogate TKI binding, leading to reduced or loss of response. They can arise at any time during the disease course because of the inherent genetic instability of *BCR-ABL1+* cells. However, Sanger sequencing - the recommended method for routine screening for *BCR-ABL1* kinase domain mutations, has a limit of detection of only 15–20%. Although NGS is known to have greater sensitivity, prior to this study, the clinical significance of low-level mutations was unknown. This study indicates that patients with NGS detected mutations have inferior PFS, and patients with early detectable mutations appear more likely to go onto have adverse outcomes including accelerated disease.

Reference: Lancet Haematol 2019;6:276–84
Abstract

Active surveillance for nodular lymphocyte-predominant Hodgkin lymphoma

Authors: Borchmann S, et al.

Summary: All patients (n=163) aged 16 years or older diagnosed with nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) at Memorial Sloan Kettering Cancer Center between 1974 and 2016 were included in this study, which compared treatment outcomes between management with active surveillance and other strategies. Patients were treated with radiotherapy alone (46%), active surveillance (23%), chemotherapy (16%), combined modality (12%), or rituximab monotherapy (4%). At median follow-up of 69 months, five-year PFS was 85%, second PFS (PFS2) was 97%, and OS was 99%, among all patients. Patients managed with active surveillance had a shorter 5-year PFS than those receiving active treatment (77% vs 87%; P=0.017), but no significant difference in PFS2 or OS. Ten patients (27%) in the active surveillance group ultimately needed treatment, after a median of 61 months, and none died.

Comment: This important and provocative study suggests that NLPHL patients with asymptomatic/low tumour burden (i.e. no disease-related symptoms or mass lesions threatening organ compromise) that are 'treated' with surveillance of do not suffer any disadvantage in terms of long-term disease control compared with active treatment. Results of this single-centre retrospective study require further validation, and given the rarity of the results this will require large-scale coordination.

Reference: Blood. 2019;133(20):2121-2129.
Abstract

Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab

Authors: Byrd JC, et al.

Summary: This paper described long-term follow-up of patients treated in RESONATE, which compared ibrutinib to ofatumumab in high-risk, relapsed patients with CLL, where superiority of PFS (HR 0.133) was observed for ibrutinib. The OS benefit for ibrutinib continues (HR 0.591), but with a lesser benefit compared to that before crossover to ibrutinib for ofatumumab patients (HR 0.426). Overall response to ibrutinib increased over time, with 91% of patients achieving a response. The PFS benefit with ibrutinib was independent of baseline risk factors, although patients with at least two previous therapies had a shorter PFS than those with less than two prior therapies, and those with *TP53* or *SF3B1* mutations trended toward a shorter PFS versus patients without these factors. At a median follow-up of 44 months, 46% of patients were still on treatment. Grade ≥3 AEs lessened over time, leading to only a few discontinuations, while ibrutinib was stopped due to disease progression in 27% of patients.

Comment: After nearly 4 years follow-up, ibrutinib was effective in all patients with R/R CLL, including high-risk CLL (del 17p, TP53 mutation, complex karyotype, and SF3B1 mutation), but as a trend not at the same level as standard-risk patients. Despite this, less than half of the patients continued therapy with ibrutinib during the observation period, due to side effects, Richter's transformation or progressive disease.

Reference: Blood. 2019;133(19):2031-2042.
Abstract

CLL2-BIG: sequential treatment with bendamustine, ibrutinib and obinutuzumab (GA101) in chronic lymphocytic leukemia

Authors: von Tresckow J, et al.

Summary: This exploratory trial examined sequential combination therapy in 61 patients with previously untreated or R/R CLL. Bendamustine was given for debulking in patients with a high tumour load, followed by induction ibrutinib and obinutuzumab, followed by maintenance until MRD. During induction, neutropenia (14.8%) and thrombocytopenia (13.1%) were the most common grade 3-4 AEs. One patient died due to duodenitis. The ORR was 100%, including 54.1% partial remission, 41% clinical complete remission without confirmation by CT scan or bone marrow biopsy and 4.9% clinical complete remission with incomplete recovery of the bone marrow. Undetectable ($<10^{-4}$) MRD was evident in 47.5% of patients, as measured by flow cytometry in peripheral blood.

Comment: This innovative trial of both treatment naïve and R/R CLL patients evaluated a sequential combination therapy of two cycles of bendamustine for debulking (in patients with a high tumour load defined as ALC ≥25 and/or nodes >5cm), followed by six courses of induction therapy with ibrutinib and obinutuzumab, and then maintenance phase which continued until MRD was confirmed. The ORR compares favourably with ibrutinib monotherapy and ibrutinib-rituximab, rates of tumour lysis syndrome were low, and MRD achievement impressive. The BIG regimen is a safe and highly effective therapy for CLL.

Reference: Leukemia. 2019;33(5):1161-1172.
Abstract

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