Lymphoma & Leukaemia Research Review™

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Issue 25 - 2018

In this issue:

- Levofloxacin prophylaxis for bacteraemia in children
- Rituximab + lenalidomide in follicular lymphoma
- Lenalidomide + R-CHOP in follicular lymphoma
- Cladribine and low-dose cytarabine alternating with decitabine in AML
- CPX-351 liposome vs cytarabine + daunorubicin in AML
- Childbearing potential in Hodgkin lymphoma
- Safety of venetoclax in R/R CLL
- Long-term follow-up of first-line ibrutinib in CLL
- B-cell lymphomas in patients on JAK1/2 inhibitors
- Moxetumomab pasudotox in R/R hairy cell leukaemia

Abbreviations used in this issue:

ALL = acute lymphoblastic leukaemia
AML = acute myeloid leukaemia
CLL = chronic lymphocytic leukaemia
DFS = disease-free survival
HCL = hairy cell leukaemia
HL = Hodgkin lymphoma
HSCT = haematopoietic stem cell transplantation
MDS = myelodysplastic syndrome
MRD = minimal residual disease
NHL = non-Hodgkin lymphoma
ORR = overall response rate
OS = overall survival
PFS = progression-free survival
R/R = relapsed/refractory
TLS = tumour lysis syndrome

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Welcome to issue 25 of Lymphoma and Leukaemia Research Review.

This month, we bring you a study from *JAMA* reporting that levofloxacin prophylaxis significantly reduces the risk of bacteraemia in children with acute leukaemia receiving intensive chemotherapy but not in those undergoing stem cell transplantation. Next up are two studies in previously untreated follicular lymphoma. The first shows that efficacy results are similar with rituximab plus lenalidomide and rituximab plus chemotherapy. The second study demonstrates that lenalidomide in combination with R-CHOP has an acceptable safety profile and anticancer activity in patients with high burden disease.

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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Effect of levofloxacin prophylaxis on bacteraemia in children with acute leukaemia or undergoing haematopoietic stem cell transplantation

Authors: Alexander S, et al.

Summary: In this study, levofloxacin prophylaxis significantly reduced the risk of bacteraemia in children with acute leukaemia receiving intensive chemotherapy but not in those undergoing HSCT. The multicentre, open-label, randomised trial, enrolled patients (6 months-21 years) receiving intensive chemotherapy into two separate groups - acute leukaemia (AML or relapsed ALL), and HSCT recipients. Patients with acute leukaemia were randomised to receive levofloxacin prophylaxis for two consecutive cycles of chemotherapy (n = 100) or no prophylaxis (n = 100). Patients undergoing HSCT were randomised to receive levofloxacin prophylaxis during one HSCT procedure (n = 210) or no prophylaxis (n = 214). The likelihood of bacteraemia in patients receiving levofloxacin prophylaxis compared with no prophylaxis was 21.9% versus 43.4% for patients with acute leukaemia (P = 0.001) and 11.0% versus 17.3% for patients undergoing stem cell transplantation (P = 0.06). Fever and neutropenia were less common in the levofloxacin group (71.2% vs 82.1%; P = 0.002).

Comment: Use of prophylactic antibiotics have the potential to reduce bacterial infections but this is tempered by the increased risk of negative consequences such as *C. difficile* diarrhoea and development of bacterial resistance. Prior to this study only data from single-arm paediatric studies were available. In this RCT, levofloxacin prophylaxis significantly reduced the risk of bacteraemia and fever (but not severe infection) in children with acute leukaemia receiving intensive chemotherapy but not in those undergoing stem cell transplantation. There was no significant increase in *C. difficile* or antibiotic resistance.

JAMA. 2018;320:995-1004.
Abstract

Rituximab plus lenalidomide in advanced untreated follicular lymphoma

Authors: Morschhauser F, et al.

Summary: Among patients with previously untreated follicular lymphoma, efficacy was similar with rituximab plus lenalidomide (R-lenalidomide) and rituximab plus chemotherapy (R-chemo), according to results of this multicentre, international, phase 3 trial. Patients (n=1030) were randomly assigned to receive one of two regimens: 18 cycles of R-lenalidomide, followed by rituximab maintenance therapy every 8 weeks for 12 cycles (six additional doses); or R-chemo (investigator's choice of one of three rituximab-based regimens), followed by maintenance rituximab every 8 weeks for 12 cycles. The rate of confirmed or unconfirmed complete response at 120 weeks was similar in the two groups: 48% in the R-lenalidomide group and 53% in the R-chemo group (P=0.13). The interim 3-year rate of PFS was 77% and 78%, respectively. More patients in the R-chemo group had grade 3 or 4 neutropenia (32% vs 50%) and febrile neutropenia of any grade (2% vs 7%), and more patients in the R-lenalidomide group had grade 3 or 4 cutaneous reactions (7% vs 1%).

Comment: This was a well-conducted study. Nearly half of the patients were high risk on the basis of their FLIPI score. PFS, response rates and transformation rate outcomes were similar between arms, but as with RELEVANCE, POD24 was unfortunately not reported. Whereas R-chemo (investigator choice of B-R, R-CHOP, R-CVP) had higher haematological toxicity, cutaneous reactions were higher with R-lenalidomide. Interestingly, FLIPI was prognostic with R-chemo but not with the chemo-free regimen, suggesting new prognostic indices may need to be established in the chemo-free setting.

N Engl J Med. 2018;379:934-947.
Abstract

Lenalidomide in combination with R-CHOP (R2-CHOP) as first-line treatment of patients with high tumour burden follicular lymphoma

Authors: Tilly H, et al.

Summary: Lenalidomide in combination with R-CHOP (R2-CHOP) had an acceptable safety profile and showed anti-cancer activity in patients with previously untreated high burden follicular lymphoma in this French study. Patients received induction therapy with six cycles of R2-CHOP every 3 weeks, followed by two rituximab infusions at 3-week intervals for a total of 24 weeks. Patients who achieved a complete or partial response to induction therapy received maintenance rituximab every 8 weeks for 2 years. Eighty patients were enrolled, and 68 completed six cycles of R2-CHOP. At the end of induction, 59 patients (74%) achieved a complete response. 55 patients (69%) achieved a complete response at 30 months from enrolment. The most common AE was grade 4 neutropenia in 65% of patients. The most common non-haematological AEs were grade 1-2 sensory neuropathy (35%) and grade 1-2 transient rash (34%).

Comment: It is important not to over-interpret this single-arm study with median follow-up of 45 months. Furthermore, in the text but not the abstract, we are informed that the anticipated primary endpoint, a target CR of 80%, was not met. It is disappointing that POD24 was not included as an endpoint, as arguably this is the more clinically relevant surrogate endpoint. R2-CHOP was associated with substantial haematological toxicity. Larger, comparative studies (perhaps against rituximab-chemotherapy or R2) with appropriate outcome measures are required to define the place of R2-CHOP in high-tumour burden follicular lymphoma.

Lancet Haematol. 2018;5:e403-e410.
Abstract

Cladribine and low-dose cytarabine alternating with decitabine as front-line therapy for elderly patients with acute myeloid leukaemia

Authors: Kadia TP, et al.

Summary: This phase 2 single-arm trial found that the combination of cladribine and low-dose cytarabine alternating with decitabine is a safe and effective regimen for the treatment of elderly or unfit patients with newly diagnosed AML. Patients (n=118) were treated with cladribine plus low-dose cytarabine (20 mg subcutaneously twice daily on days 1-10) for two 28-day cycles alternating with decitabine for two 28-day cycles, for up to 18 cycles. Median DFS was 10.8 months and median OS was 13.8 months. Eighty (68%) patients achieved an objective response including 69 (58%) with a complete response and 11 (9%) with a complete response and incomplete count recovery. The most common non-haematological AEs ≥ grade 3 were infection (75%), elevated total bilirubin (22%), rash (11%), and nausea (11%). There was one (1%) death within the first 4 weeks and eight (7%) deaths within the first 8 weeks.

Comment: Single-agent hypomethylating agents are associated with substantial haematological toxicity but relatively low non-haematological toxicity (but with limited safety margins). Hence many trials are currently investigating the addition of various agents to a hypomethylating backbone as treatment for elderly and frail patients. Decitabine and cladribine trigger DNA hypomethylation by different and complementary mechanisms and also have a distinct mode of action to cytarabine. The investigators take advantage of this to use a rotating multiagent regimen, a concept widely used in oncology. The regimen was well-tolerated and results warrant further investigation.

Lancet Haematol. 2018;5:e411-e421.
Abstract

CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukaemia

Authors: Lancet JE, et al.

Summary: CPX-351 treatment was associated with significantly longer survival and similar tolerability compared with conventional cytarabine plus daunorubicin chemotherapy in older adults with newly diagnosed secondary AML (sAML) in this open-label, randomised, phase 3 trial. 309 patients age 60 to 75 years received one to two induction cycles of CPX-351 or standard cytarabine plus daunorubicin (7+3 regimen) followed by consolidation therapy. CPX-351 significantly improved median OS (9.56 vs 5.95 months; P = 0.003) and overall remission rate (47.7% vs 33.3%; P = 0.016), versus 7+3. Improved outcomes were seen across age groups and AML subtypes. The incidences of nonhematologic AEs were similar between groups, despite a longer treatment phase and prolonged time to neutrophil and platelet count recovery with CPX-351. Early mortality rates with CPX-351 and 7+3 were 5.9% and 10.6% (P = 0.149) through day 30 and 13.7% and 21.2% (P = 0.097) through day 60.

Comment: CPX-351 is a dual-drug liposomal encapsulation of cytarabine and daunorubicin at a fixed 5:1 synergistic molar ratio. It is designed to enhance uptake in leukaemia cells to a greater extent than normal cells. In animal models, it has superior antileukaemia activity compared to the free drugs administered at the same ratios. This is because a 5:1 ratio cannot be sustained through free cytarabine and daunorubicin administration because they have different pharmacokinetics. Another potential benefit is that entry of cytotoxics via intact liposomes may bypass drug-resistance efflux pumps. The results of this study recently led to FDA approval for treatment of adults with newly diagnosed therapy-related AML or sAML. It will be interesting to see future studies comparing CPX-351 in combination with small-molecule inhibitors (e.g., midostaurin, venetoclax) and/or antibody drug conjugates.

J Clin Oncol. 2018;36:2684-2692.
Abstract

Contemporarily treated patients with Hodgkin lymphoma have childbearing potential in line with matched comparators

Authors: Weibull CE, et al.

Summary: This Swedish study reports that childbearing potential among female survivors of HL has improved over time, and childbirth rates 3 years after diagnosis are, in the absence of relapse, similar to those in the general population. 449 women diagnosed with HL between 1992 and 2009 and in remission 9 months after diagnosis were identified. Patients were matched to 2,210 population comparators. Twenty-two percent of relapse-free patients with HL had a child during follow-up, and first childbirth rates increased over time, from 40.2 per 1000 person-years (1992 to 1997) to 69.7 per 1000 person-years (2004 to 2009). For comparators, childbirth rates remained stable (70.1 per 1000 person-years). Three years or more after diagnosis, no differences in childbirth rates were observed between patients and comparators, regardless of stage or treatment. Patients who received BEACOPP had a lower childbirth rate than comparators during the first 3 years, as did patients who received chemotherapy and radiotherapy.

Comment: In this important Swedish registry study of childbearing among female survivors of HL over different time periods, relapse-free women treated in the modern era had birth rates similar to those in the general population from 3 years after diagnosis onward, regardless of stage and primary treatment. Even after treatment with what is considered the most gonadotoxic chemotherapy combination, BEACOPP, childbirth rates, although reduced during the first 3 years, later on approached that of the comparable general population. There was no increased risk of HL relapse after pregnancy and the health of the children did not appear adversely effected.

J Clin Oncol. 2018;36:2718-2725.
Abstract

Lymphoma and Leukaemia Research Review™

Independent commentary by Maher Gandhi
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FL: follicular lymphoma; CLL: chronic lymphocytic leukaemia; SLL: small lymphocytic lymphoma.

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References: 1. Pharmaceutical Benefits Schedule. Available at: www.pbs.gov.au. Accessed September 2017.
2. Zydelig Product Information, 26 October 2017.

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Comprehensive safety analysis of venetoclax monotherapy for patients with relapsed/refractory chronic lymphocytic leukaemia

Authors: Davids MS, et al.

Summary: Venetoclax 400 mg/day as a long-term continuous therapy is generally well tolerated in patients with R/R CLL according to this analysis of three phase I/II studies (n=350). Median age was 66 years, 60% of patients had del(17p), and patients had received a median of three prior therapies. The most common grade 3/4 AEs were neutropenia (37%), anaemia (17%), and thrombocytopenia (14%). Grade 3/4 neutropenia was manageable with growth factor support and dose adjustments; the incidence of serious infections in these patients was 15%. With the current 5-week dose increase, the incidence of laboratory TLS was 1.4%, none had clinical sequelae, and all of these patients were able to increase to a daily dose of 400 mg. Ten percent of patients discontinued venetoclax due to AEs and 8% died while on study, mostly due to disease progression.

Comment: The use of venetoclax is increasing in clinical practice and a detailed analysis of its toxicity profile is important, particularly as dosing is likely to be for prolonged periods. Of particular note in this study, with a 5-week ramp up, hydration and oral uric acid-reducing agents the TLS rates were <2%. The onset and severity of new AEs decreased over time; however, low-grade GI-toxicity was persistent in the patients that initially experienced this. Growth factor support +/- dose adjustments effectively mitigated against risk of infections and the types of infections were in the range of what would be expected for a group of heavily pre-treated patients with CLL. Opportunistic infections were reported in 11 patients (3.1%), three of which were serious. However, there were no deaths related to opportunistic infections and two of the three resumed venetoclax.

Clin Cancer Res. 2018;24:4371-4379.
Abstract

Sustained efficacy and detailed clinical follow-up of first-line ibrutinib treatment in older patients with chronic lymphocytic leukaemia

Authors: Barr PM, et al.

Summary: These extended phase 3 results from RESONATE-2 demonstrate that first-line ibrutinib for elderly patients with CLL provides sustained response and PFS benefits over chemotherapy, with depth of response improving over time without new toxicity issues. A total of 269 patients aged ≥65 years with previously untreated CLL without del(17p) were randomised to receive ibrutinib or chlorambucil. Median ibrutinib treatment duration was 28.5 months. Median PFS was significantly prolonged in the ibrutinib group compared with the chlorambucil group (not reached vs 15 months; P<0.0001). ORR was 92% in the ibrutinib group and complete response improved from 7% at 12 months to 18% with longer follow up. Quality of life as measured by Functional Assessment of Chronic Illness Therapy-Fatigue was significantly greater with ibrutinib compared to chlorambucil (P=0.0013). The most common grade ≥3 AEs were neutropenia (12%), anaemia (7%), and hypertension (5%). Rate of discontinuations due to AEs was 12%.

Comment: RESONATE-2 (Burger, NEJM 2015) tested efficacy and safety of first-line ibrutinib in older patients with CLL without del(17p) against chlorambucil. Its findings (84% reduction in the risk of death at 18 months) led to FDA approval. This extended follow-up (28.5 months) study demonstrated that first-line ibrutinib provides sustained response and benefits over chlorambucil, with depth of response improving over time without new toxicity concerns.

Haematologica. 2018;103(9):1502-1510.
Abstract

Aggressive B-cell lymphomas in patients with myelofibrosis receiving JAK1/2 inhibitor therapy

Authors: Porpaczy E, et al.

Summary: This study examined 626 patients with myeloproliferative neoplasms (MPN) receiving JAK1/2 inhibitors, for lymphoma development. B-cell lymphomas evolved in 4 (5.8%) of 69 patients receiving JAK1/2 inhibitors compared with 2 (0.36%) of 557 treated with conventional treatment (16-fold increased risk). Looking at only primary myelofibrosis (n=216), 3 lymphomas developed in 31 inhibitor-treated patients (9.7%) versus 1 (0.54%) of 185 control patients. Median time from starting inhibitor therapy to lymphoma diagnosis was 25 months. Lymphomas were of aggressive B-cell type, extranodal, or leukaemic with high MYC expression in the absence of *JAK2* V617F or other MPN-associated mutations. Clonal immunoglobulin gene rearrangements were already detected in the bone marrow during myelofibrosis in 16.3% of patients. A pre-existing B-cell clone preceded lymphoma development during JAK1/2 inhibitor treatment in all 3 patients tested. Sequencing verified clonal identity in 2 patients.

Comment: Ruxolitinib (an inhibitor of both JAK1 and JAK2) is available on the PBS in patients with primary and secondary myelofibrosis and more recently has been approved by the FDA for the treatment of polycythemia vera in patients intolerant of hydroxyurea. However, sporadic observations have raised concerns that there may be an increased risk of B-cell lymphomas. Using a discovery and validation cohort approach, with findings then reproduced in a murine model, this elegant study finds a 15-16-fold risk of high MYC expressing B-NHL in blood and marrow, that seems to be related to a pre-existing B-cell clone within the marrow. Further study to understand the mechanistic basis for this observation is needed, and patients should be adequately informed of the risks.

Blood. 2018;132:694-706.
Abstract

Moxetumomab pasudotox in relapsed/refractory hairy cell leukaemia

Authors: Kreitman RJ, et al.

Summary: Moxetumomab pasudotox led to a high rate of independently assessed durable response and MRD eradication in heavily pretreated patients with HCL, with acceptable tolerability, in this pivotal, open-label study. Patients received moxetumomab pasudotox 40 µg/kg intravenously on days 1, 3, and 5 every 28 days for ≤6 cycles. Response and MRD status were evaluated by blinded independent central review. Among 80 patients the most common AEs were peripheral oedema (39%), nausea (35%), fatigue (34%), and headache (33%). Treatment-related serious AEs of haemolytic uremic syndrome (7.5%) and capillary leak syndrome (5%) were reversible and manageable with supportive care and treatment discontinuation (6 patients; 7.5%). Durable complete response rate was 30%, complete response rate was 41%, and objective response rate (complete and partial) was 75%; 64 patients (80%) achieved haematologic remission. Among complete responders, 27 (85%) achieved MRD negativity by immunohistochemistry.

Comment: Although current therapies are highly effective in HCL, roughly 50% of patients will eventually relapse due to presence of MRD. Moxetumomab pasudotox is a recombinant immunotoxin targeting CD22 fused to Pseudomonas exotoxin PE38. In this, the largest prospective study of multiply relapsed or refractory HCL, the antibody drug conjugate achieved a high rate of independently assessed durable response and bone marrow MRD eradication in heavily pre-treated patients with HCL, with acceptable tolerability. Interestingly, the high rate of clinical activity was observed despite a high rate of immunogenicity (~75% of patients had detectable neutralizing antibodies at the end of treatment). Haemolytic uraemia and capillary leak syndromes remain a concern.

Leukemia. 2018;32:1768-1777.
Abstract

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