INSIDE
Improving Patient Outcomes in Acute Leukaemias: Navigating Complex Treatment Decisions in an Era of Novel Therapies

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Improving Patient Outcomes in Acute Leukaemias: Navigating Complex Treatment Decisions in an Era of Novel Therapies

This symposium took place on 14th June 2019, as part of the 24th European Hematology Association (EHA) Annual Congress in Amsterdam, Netherlands

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Meeting Summary

Dr Janssen presented the changing treatment landscapes in acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL). Data showed that advancements in the treatment of ALL have improved survival rates. The more intensive paediatric-based regimens implemented for patients with ALL up to 40 years of age have advantaged younger populations while poor survival rates persist for older patients (Figure 1).1 Dr Janssen introduced emerging B-cell (B)-ALL therapies, including blinatumomab,2 inotuzumab ozogamicin,3 and tisagenlecleucel,4 and the array of recent approvals for AML. He also introduced a number of Phase III studies for patients with AML which have been organised by the Haemato Oncology Foundation for Adults in the Netherlands (HOVON) and are at various stages of development.

Dr Röllig detailed treatment algorithms to aid selection of front-line de novo AML therapy. He addressed the controversy surrounding waiting times for cytogenetic results, and how these results can be used when making treatment decisions in AML. Selection of treatment was demonstrated in
three clinical cases. The first case of an older patient with core binding factor (CBF)-AML showed how the decision between non-intensive and intensive treatment is dependent on chance of remission/cure and cytogenetics, as well as age, comorbidities, and performance status. The second case discussed the impact of patient and disease factors in deciding treatment for a patient with AML with myelodysplastic features. The third case was of a younger patient with NPM1 mutation, FLT3- internal tandem domain (ITD) mutation, and invasive hyperleukocytosis in a situation when immediate intensive chemotherapy was necessary. Discussion around the treatment choice centered around the relapse risk in a patient with FLT3-ITD and low allelic ratio, the prognosis of patients who do not receive HSCT, and the prognostic value of having mutated NPM1 status.

Dr Cassaday focussed on therapy selection in relapsed/refractory ALL. While choice of therapy is guided by factors impacting therapy goals, minimal residual disease (MRD) status is vital. Evidence for use of blinatumomab, inotuzumab ozogamicin, tisagenlecleucel, and ponatinib was summarised. Blinatumomab achieved high response rates (43.9% complete remission [CR] or CR with incomplete haematologic recovery [CRh]), particularly in patients with low disease burden (<50.0% bone marrow blasts; 73.0%), making it a therapy option for this subgroup. Additionally, blinatumomab presented a favourable tolerability profile. Inotuzumab ozogamicin also achieved high response rates (80.7% CR/CR with incomplete haematological recovery [CRI]), and there was only a minimal difference between patients with high (77.9%) and low (86.7%) disease burden (>50% blast count = high disease burden, <50% = low disease burden). Of concern with inotuzumab ozogamicin is veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS). Studies of tisagenlecleucel indicated high rates of overall remission and event-free survival (EFS), but it can cause serious toxicity (cytokine release syndrome [CRS] and neurotoxicity). Although ponatinib was fairly well-tolerated, the probability of staying in remission was low (sustained response rate at ≥12 months of 8.0%).

Treatment Landscapes in Acute Myeloid Leukaemia and Acute Lymphoblastic Leukaemia

Doctor Jeroen Janssen

Advancements in the treatment of ALL including regimens of increasing intensity as in paediatric protocols, drugs for Philadelphia (Ph)-positive patients, and cellular therapy, have improved survival rates. Data from the Netherlands Cancer Registry show that older patients with ALL have not particularly benefited from these improvements. Five-year overall survival (OS) between the years 2007 and 2012 among patients aged 18–39 years was 68% for those receiving chemotherapy and 66% for those receiving allogeneic-HSCT; for patients aged 40–69 years, comparable estimates were 24% and 41%. The marked improvement seen in younger people was not reflected in the older group (Figure 1). Moreover, compared with the general population, survival rates of older patients aged 60–69 and ≥70 years of 22% and 5%, respectively, indicated very poor outcomes. These findings were reflected among adults aged ≥60 years in the Surveillance, Epidemiology, and End Results (SEER) Program.

Tyrosine kinase inhibitors (TKI) are effective in the targeted treatment of patients with Ph-positive B-ALL, with studies demonstrating long-term survival rates increasing from <20% to ~75%. A study combining hyperCVAD (hyperfractionated cyclophosphamide/vincristine/doxorubicin/dexamethasone) with ponatinib for patients with Ph-positive ALL demonstrated early sustained remissions, with a 2-year EFS rate of 81%; all patients achieved a MRD-negative status by 9 months.

MRD is regarded as a strong, independent predictor of long-term remission and survival in ALL. A prospective evaluation of molecular response estimated that the survival probability for patients with a molecular complete response (MRD-negative) was 80% compared with 42% of patients with molecular failure (MRD-positive). Persistent, quantifiable MRD positivity within the quantitative range (≥10−4) was defined as ‘molecular failure’ (molFail), and reappearance of MRD within the quantitative range (>10−4) after prior achievement of molecular CR was defined as molecular relapse.
Emerging therapies for B-ALL include blinatumomab, inotuzumab ozogamicin, tisagenlecleucel, and, for relapsed T-cell ALL, nelarabine.

Treatment for AML has lagged behind that for ALL, although more recently drugs have begun to emerge, including FLT-3 inhibition (midostaurin), antibody-drug conjugation (gemtuzumab ozogamicin), and drug reformulation (CPX-351; daunorubicin/cytarabine).

In collaboration with European AML study groups, HOVON20 have embarked on Phase III studies for patients with AML that are at various stages of completion.

Figure 1: Survival improvement among patients aged 18–39 years might mainly be explained by implementation of increasing intensity paediatric-based regimens since 2005.

CI: confidence interval; No.: number; OS: overall survival.


Improving Patient Outcomes Through Optimal Therapy Selection in Relapsed/Refractory Acute Lymphoblastic Leukaemia

Doctor Ryan Cassaday

Treatment options for relapsed or refractory (R/R) B-ALL are more complicated than those for front-line therapy. While there is still a role for standard multi-agent chemotherapy combinations, there is increasing interest in the targeted agents for R/R B-ALL.

Antibody-based agents include blinatumomab and inotuzumab ozogamicin. A potential therapy milestone is the CD19 (CAR) T-cell therapy tisagenlecleucel. Moreover, resistance among ABL kinase inhibitors has led to the development of ponatinib for patients with Ph-positive ALL.

Choice of therapy for patients with R/R ALL is guided by the goal of therapy and the patient and disease factors. Disease factors such as response to front-line therapy, prior stem cell transplantation, and disease burden may impact treatment choice. Patient factors such as comorbidities are important for assessing therapy intensity and the potential for adverse events. Furthermore, the costs and logistics of giving each therapy should also be considered.

The majority of patients with ALL who achieve CR will relapse, although second remissions can be achieved with further therapy. A post-hoc analysis of the UKALL 12/ECOG2993 study found that therapy received during the first CR (CR1) did not influence outcome after relapse.
MRD is most important for assessing prognosis. A retrospective study of adults with ALL who had achieved MRD-negative status in CR1 following adult-inspired therapy demonstrated OS was similar with or without HSCT. Furthermore, HSCT in patients with MRD-negative status in second CR could also achieve long-term OS. MRD-negativity provides a baseline from which to use HSCT and aim for continued remission.

Blinatumomab is a bispecific T-cell engager antibody construct targeting CD19. In the TOWER trial in adults with heavily pre-treated B-ALL, remission rates with respect to CR with full, partial, or incomplete haematologic recovery were significantly higher in the blinatumomab group than in the standard therapy group (p<0.001). The majority of remissions achieved a MRD-negative status (76% versus 48%, respectively) and numbers proceeding to HSCT were comparable (24% in both groups). OS was significantly longer in the blinatumomab group versus standard therapy (HR death: 0.71; p=0.01), although the survival advantage was no longer evident after 15 months.

A separate Phase II study of patients with Ph-negative, primary R/R ALL treated with blinatumomab regardless of number of previous salvage therapies and previous HSCT found that 43% of patients had a CR/CRh (CR with partial recovery of peripheral blood counts) during the first two cycles of blinatumomab. Notably, patients with low disease burden (<50.0% bone marrow blasts) had a much higher chance of achieving morphological remission (73% CR/CRh rate) versus those with a high disease burden (≥50.0% bone marrow blasts)(29.0% CR/CRh rate), suggesting that blinatumomab may be most beneficial where disease burden is low.

Inotuzumab ozogamicin is another targeted agent, a CD22-directed antibody conjugated to calicheamicin. The INO-VATE ALL trial reported high rates of remission and MRD-negativity among patients with R/R, CD22-positive, Ph-positive, or Ph-negative ALL treated with inotuzumab ozogamicin versus standard therapy. The CR/CRi rate was significantly higher in the inotuzumab ozogamicin group than in the standard therapy group (80.7% versus 29.4%; p<0.001) and, of the patients in CR, a higher proportion in the inotuzumab ozogamicin group had below-threshold MRD levels (78.4% versus 28.1%; p<0.001). The proportion of patients in the inotuzumab ozogamicin group with low disease burden (<50.0% bone marrow blasts) had a similar chance of achieving morphological remission versus those with a high disease burden (≥50.0% bone marrow blasts); (86.7% versus 77.9%). There was also a significant difference in the proportion of patients proceeding directly to HSCT following study treatment (42.6% versus 11.1%; p<0.001). The adjusted total rates including those patients who had subsequent therapies after study treatment and before HSCT were 48.2% versus 22.2%. The OS advantage for patients treated with inotuzumab ozogamicin (versus standard therapy) at 2 years (p=0.0004) continued to the third year (p=0.0093).

The INO-VATE study revealed a safety concern for inotuzumab ozogamicin, with VOD/SOS occurring in 14.0% patients receiving this agent. Factors likely to increase the risk of VOD/SOS after inotuzumab ozogamicin treatment included a dual-alkylating agent conditioning regimen, high pre-HSCT bilirubin concentration, high pre-HSCT aspartate aminotransferase/alanine aminotransferase concentration, and a history of liver disease/hepatitis.

An INO-VATE ALL trial post-hoc analysis determined that among subgroups of inotuzumab ozogamicin-treated patients OS at 24 months was higher for those receiving their first allogenic HSCT (45.7%) and those receiving their first allogenic HSCT and having achieved CR/CRi before transplant (51.1%). Patients with no previous transplant who proceed directly to HSCT following study treatment (42.6% versus 11.1%; p<0.001). The adjusted total rates including those patients who had subsequent therapies after study treatment and before HSCT were 48.2% versus 22.2%. The OS advantage for patients treated with inotuzumab ozogamicin (versus standard therapy) at 2 years (p=0.0004) continued to the third year (p=0.0093).

The CAR T-cell therapy tisagenlecleucel is an autologous immunotherapy for the treatment of R/R B-ALL. The single-arm ELIANA trial investigated tisagenlecleucel in children and young adults with CD19+ R/R B-ALL. In the 75 patients who received tisagenlecleucel and had ≥3 months follow-up, overall remission rate was 81%, of which 60% had CR and 21% had CRi. The EFS rate was 73% at 6 months and 50% at 12 months; median EFS was not reached.

The ELIANA trial tisagenlecleucel safety profile indicated potential serious toxicity. CRS occurred in 77% (of 75 patients), with almost half (47%) admitted for intensive care. Grade 3 neurotoxicity events occurred in 13% of patients.
Regarding use of the BCR-ABL kinase inhibitor ponatinib\(^9\) for R/R Ph-positive ALL, a Phase II study showed 41% of patients had a major haematological response, with a median duration of 3 months.\(^{10}\) The probability of staying in remission was low, with the sustained response rate at ≥12 months of 8%.\(^{10}\) Ponatinib was generally well tolerated with a <20% incidence of Grade 3/4 cytopenias; rare occurrence of non-haematologic grade 3/4 events; and serious arterial thrombotic events in only 9% of patients.\(^{10}\)

Clinical Use of Some of These Therapies is Best Exemplified in a Case History

Front-Line Therapy

This patient was diagnosed with Ph-negative B-ALL at 35 years old and began treatment with hyperCVAD. She was MRD-positive (0.02%) after cycle 1A but was MRD-negative after cycle 2B. Because achieving MRD-negativity early is an independent predictor for EFS,\(^{30}\) HSCT was deferred during CR1. She completed the full treatment course and was given POMP (6mercaptopurine/vincristine/methotrexate/prednisone) maintenance therapy for 2 years.

Relapsed Disease

At 1 year after completing maintenance therapy, she presented with progressive fatigue and petechiae. Laboratory investigations revealed pancytopenia, a disease burden of 78% B lymphoblasts, and notable immunophenotypic features (CD19+, CD22+). She had no other signs, and expressed a wish for aggressive, curative-intent treatment, and for hospitalisation avoidance.

Salvage Therapy

The patient was started on inotuzumab ozogamicin\(^3\) because of its high response rate versus standard therapy and potential for outpatient-based administration. This was tolerated well by the patient.\(^{3,7}\) Bone marrow examination after recovery revealed morphological CR, but she was MRD-positive (0.4% B-lymphoblasts). She was then given blinatumomab.\(^2\) This was also tolerated well, with fever on infusion Day 1, but no other signs of CRS or neurotoxicity. A bone marrow examination after completion showed that she was MRD-negative. The patient was referred for HSCT from her human leukocyte antigen-identical sister. A conditioning regimen consisting of total body irradiation plus cyclophosphamide, with methotrexate and tacrolimus for graft versus host disease prophylaxis, was used. This patient is still in remission.

To summarise, several effective therapies have been approved in the past ~5 years for the treatment of R/R B-ALL, including blinatumomab,\(^2\) inotuzumab ozogamicin,\(^3\) and tisagenlecleucel.\(^4\) However, their unique side-effect profile must be considered on an individual patient basis. Blinatumomab and CAR T-cells can cause CRS and neurotoxicity,\(^{5,8}\) while VOD/SOS is a potential adverse event with inotuzumab ozogamicin.\(^7\) Other treatment options, such as multi-agent chemotherapy\(^{21}\) and ponatinib,\(^9\) also have a role in R/R B-ALL therapy. Nevertheless, despite these advances, improvements in therapy are still needed and these need to be evaluated in clinical trials.

Closing Remarks

Doctor Jeroen Janssen

There are promising targeted drugs for AML with specific molecular aberrations but this only constitutes a subset of all patients with AML and we are still working to better define their roles in AML treatment. In the current management of AML, it becomes ever-more crucial to identify which patients will benefit from intensive treatment, while the addition of antibody-drug conjugates to the therapeutic armamentarium for the AML subset with favourable/intermediate-risk features provides a valuable option in patients treated intensively.\(^{18}\) Effective immunotherapeutic drugs\(^2-4\) have been developed for patients with ALL; however, within Europe, the costs of these new therapies are often prohibitive.
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