Outlook for 2017: Acute Leukemias, MDS, and CLL

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This look ahead at hematologic malignancies in 2017 focuses on new agents being studied for the treatment of acute leukemias, myelodysplastic syndromes, and chronic lymphocytic leukemia.

Acute Leukemias and Myelodysplastic Syndromes

Steven T. Rosen, MD, served as series editor for this two-part series on hematologic malignancies in 2017.

Although the vast majority of adult patients with acute leukemias or myelodysplastic syndromes (MDS) are not cured, considerable progress has been made in understanding the biology of the diseases, particularly in the use of molecular profiling to classify and predict the clinical risk of individual patients, and in the development of novel molecular targeting therapeutics.[1] Furthermore, harnessing the immune system with monoclonal antibodies, immune checkpoint inhibitors, or engineered T cells (ie, chimeric antigen receptor [CAR] T cells) has led to exciting preliminary results. Thus, a significant increase in the cure rate is expected for these patients in the near future.

Acute myeloid leukemia

In acute myeloid leukemia (AML), the role of minimal residual disease (MRD) for treatment guidance is expanding, using both specific molecular markers (eg, NPM1 mutations) or high-resolution immunophenotyping.[2,3] Assessment of MRD at defined time points after initial treatment is being tested both as a surrogate endpoint for early disease response and for guidance in the selection of subsequent therapies. Furthermore, specific molecular markers detected at diagnosis have also been shown to predict disease response to either nontargeting or molecular-targeted therapies.[4-6] TP53 mutation has recently been reported to be associated with a better response to the hypomethylating agent decitabine,[4] while in a large randomized clinical trial of FLT3/ITD and FLT3/TKD AML patients, Stone et al[5] reported a significant clinical benefit in patients treated with a tyrosine kinase inhibitor (TKI) and chemotherapy vs placebo and chemotherapy, regardless of whether they subsequently received transplant or not. Evidence of clinical response has been shown with IDH2 inhibitors in AML patients harboring IDH2 mutation, and the use of these agents is being expanded to MDS and tested in combination with chemotherapy or a hypomethylating agent in AML.[6] The critical relevance of targeting aberrantly antiapoptotic pathways in AML blasts has been demonstrated by exciting results with the BCL2 inhibitor venetoclax alone or in combination with a hypomethylating agent[7,8]. Although in the near future, the number of molecular targeting agents is expected to increase exponentially, the role of immunology-based approaches will broaden the therapeutic armamentarium for AML and MDS patients. Excellent clinical responses to the antibody-drug conjugate SGN-CD33A (vadastuximab talirine) alone or in combination with a hypomethylating agent[9] have been observed in AML patients, and immune checkpoint inhibitors and engineered CAR T cells are currently being tested. Nevertheless, even without specific molecular or immune approaches, adequate liposomal-based reformulation of conventional chemotherapeutics has provided clinical benefit in high-risk AML, underscoring the power of optimal drug delivery and over-time exposure.[10]

MDS

Except for patients with del(5q) syndrome who respond relatively well to lenalidomide, developing new pharmacologic treatments for MDS that can achieve significant response has been challenging. While several compounds with promising responses in AML are now being evaluated in MDS,[11] optimization of oral formulations of hypomethylating agents may also have a favorable impact by increasing compliance to treatment, decreasing side effects, and hopefully improving response
Acute Lymphoblastic Leukemia

Major progress has been made in childhood acute lymphoblastic leukemia (ALL), where excellent cure rates are achieved without the use of any new drugs, but by simply adhering strictly to timely drug delivery. This has prompted a similar approach in adolescent and younger adult patients with excellent results.[13,14] Furthermore, learning the genomic landscape of adult ALL has led to the recognition of new molecular subsets of the disease (ie, Philadelphia chromosome [Ph]-like ALL) and identification of novel actionable targets.[15,16] Treatment of Ph-positive ALL with a TKI and steroids alone or a TKI with chemotherapy has produced excellent responses, and although one may question whether these patients require further treatment if they achieve molecular complete response, we still advocate for hematopoietic stem cell transplantation for the vast majority of them.[17,18]

The therapeutic benefit of monoclonal antibodies has been clearly demonstrated in ALL. Expression of CD20 is seen in about 30% of B-cell ALL cases and the addition of the anti-CD20 monoclonal antibody rituximab was reportedly associated with a significant clinical benefit when combined with a pediatric-inspired regimen.[19] Blinatumomab, a bi-specific (CD3/CD19) T cell-engaging antibody that approximates CD3-positive T cells to CD19-positive B cells, has shown potent activity in patients with morphologic relapsed/refractory ALL.[20] Inotuzumab is a monoclonal antibody linked to calicheamicin that targets CD22, an antigen expressed in over 90% of B-cell ALL cases. In a phase III randomized study, single-agent inotuzumab ozogamicin was associated with significant benefit compared with standard intensive chemotherapy in relapsed/refractory adult ALL.[21]

Finally, CAR T cells, which are generated by transducing the receptor of interest in order to direct T cells toward target cells, have produced excellent results. The most successful experience so far has been with CD19-directed CAR T cells in advanced ALL.[22,23] Other CAR T cells are being engineered to target novel antigens in ALL, AML, and MDS, and it is likely that the combination of these approaches with molecular targeting agents will translate into significant clinical benefits in the near future.

Chronic Lymphocytic Leukemia

There were quite a few studies presented at both the American Society of Hematology (ASH) 2015 and 2016 meetings that investigated multiple novel agents and combinations for chronic lymphocytic leukemia (CLL). This April, venetoclax was approved by the US Food and Drug Administration for del(17p) CLL based on results from a phase II study of 106 relapsed/refractory patients who had an overall response rate of nearly 80%.[24]

Results from ASH 2016

At this year’s ASH meeting, data were presented on Juno’s anti-CD19 CAR T-cell therapy,[25] which was tested in 21 CLL patients and showed an overall response rate of 70% to 80%. Patients who achieved a complete or partial response had significantly better progression-free and overall survival. Also, researchers from the University of Pennsylvania presented data on biomarkers of response to their CD19 CAR T-cell therapy (CTL019), which had previously showed an overall response rate of approximately 50% in 41 CLL patients.[26] Lenalidomide maintenance after frontline therapy significantly prolonged progression-free survival in high-risk patients, according to an interim analysis of the German CLL Study Group’s CLL M1 trial. Progression-free survival was not reached compared with 14.6 months in the placebo group at a median observation time of 17.7 months ($P < .00001$). Overall survival was not statistically different thus far.[27] In the second-line setting (CONTINUUM trial), lenalidomide maintenance did better than placebo, with a median progression-free survival of 33.9 months vs 9.2 months at the median observation time of approximately 31 months ($P < .0001$).[28]

Idelalisib added to bendamustine and rituximab showed significant progression-free survival benefit compared with bendamustine and rituximab plus placebo (23 vs 11.1 months; $P < .0001$) and overall survival benefit (median overall survival not reached vs 40.6 months; $P = .036$). However, there were more grade 3 or higher adverse events (95% vs 78%) as well as serious adverse events (71% vs 45%), including episodes of Pneumocystis jiroveci pneumonia and cytomegalovirus in addition to late diarrhea, transaminitis, and neutropenia.[29]

Treatment with venetoclax in patients who previously received ibrutinib ($n = 43$) or idelalisib ($n = 21$) resulted in overall response rates of 60% to 70%, but produced few complete responses; estimated progression-free survival was 80% with a median follow-up of 11.8 months. Median
progression-free and overall survival rates were not reached. Forty-five percent of evaluable patients in the trial achieved MRD negativity.[30] In a trial of acalabrutinib in patients who could not tolerate ibrutinib (n = 33), the overall response rate among 29 evaluable patients was 79%, with the duration of response lasting 12 months or longer. There was only one complete response.[31] A phase Ib/II trial of obinutuzumab and ibrutinib plus venetoclax for up to 14 cycles in relapsed/refractory CLL patients (n = 12) showed two complete responses; four of ten patients who achieved partial response had MRD negativity in the bone marrow and seven had MRD negativity in peripheral blood by cycle 9. Neutropenia was a common adverse event, but there were no grade 3/4 infections, dose-limiting toxicities, or instances of tumor lysis syndrome. Phase II cohorts are ongoing.[32] TGR-1202 is a PI3K delta inhibitor with a different structure than idelalisib or duvelisib, and therefore results in milder toxicities. In a trial of TGR-1202 plus ibrutinib in relapsed/refractory CLL (n = 18), there was an 88% overall response rate among 17 evaluable patients (6% achieved a complete response). At 11 months’ follow-up, the estimated 1-year progression-free and overall survival were each 94%. [33] In a study of BGB-3111, a novel Bruton TKI, 46 patients with CLL or small lymphocytic lymphoma had an overall response rate of 96% (no complete responses) with no evidence of disease progression at a median follow-up of 8.6 months. Grade 3/4 neutropenia was observed in 9% of patients, and 2% had grade 3/4 bleeding events.[34] There are a few important trials on the horizon that we should also be watching: • Pharmacycics phase II trial of frontline ibrutinib plus venetoclax • Stanford/City of Hope phase I trial of ibrutinib plus venetoclax in relapsed/refractory patients • Acerta phase III trial of acalabrutinib (ACP-196) vs ibrutinib In addition to ongoing combination studies and MRD analyses on whether novel therapies can be stopped after 1 to 2 years, CAR T-cell studies, especially among multiple relapsed and high-risk patients, will be important to pursue. We must also find ways to better address the devastating Richter transformation. At ASH 2016 there was a presentation of an ongoing trial of acalabrutinib in patients with Richter transformation that has thus far shown an overall response rate of 38% in 29 patients. Median progression-free survival, however, is only 3.2 months. There is clearly still an unmet need for CLL patients who develop this serious complication.[35] 

References:
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