Expert Perspective on ASH 2014: Leukemia

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More than 20,000 attendees from around the world gathered at the 2014 Annual Meeting and Exposition of the American Society of Hematology (ASH), which convened on December 6, 2014, at the Moscone Center in San Francisco. The 4-day meeting is widely regarded as the foremost event in malignant and nonmalignant hematology for both physicians and scientists working in the field.[1]

Abstracts presented at this year's meeting signaled evolutions in treatment algorithms and provided attendees with a glimpse into what the future of clinical practice may look like, as heralded by the promise of exciting new agents in development. This review presents highlights of key abstracts in leukemia (see the January 2015 issue for highlights in lymphoma).

Sorafenib as Add-on to Standard Induction and Consolidation in AML

Results from the SORAMFL trial, which tested sorafenib versus placebo as add-on therapy to standard induction and consolidation treatment in patients 60 years or younger with acute myelogenous leukemia (AML), indicated that the addition of sorafenib significantly prolonged event-free survival (EFS) and relapse-free survival (RFS) in this patient subset. There were no differences in overall survival (OS).[2]

Patients ranging in age from 18 to 60 years with newly diagnosed AML were enrolled in the trial, which spanned 25 centers. All patients received 2 cycles of induction with daunorubicin (DA) plus cytarabine, followed by 3 cycles of high-dose cytarabine consolidation. Patients who showed no response following DA received a second induction with cytarabine plus mitoxantrone. All intermediate-risk and high-risk patients were scheduled to undergo allogeneic stem cell transplantation during first complete remission (CR).[2]

Patients were randomized to receive either sorafenib 800 mg/day (n = 134) or placebo (n = 133) as add-on to standard treatment in a double-blinded fashion. The trial's primary endpoint was EFS, with an event being defined as failure to achieve a CR after induction, relapse, or death. Secondary endpoints included RFS, OS, CR rate, and incidence of adverse events (AEs).[2]

Rates of CR were similar between treatment arms; specifically, 59% in the placebo arm versus 60% in the sorafenib arm (P = .764). After a median observation time of 36 months, median EFS was 9.2 months in the placebo arm versus 20.5 months in the sorafenib arm, corresponding to a 3-year EFS of 22% versus 40% (P = .013), respectively. Median RFS was 23 months after standard treatment plus placebo, but had not yet been reached after sorafenib treatment; this corresponded with 3-year RFS rates of 38% and 56% (P = .017), respectively. The 3-year OS rate was 56% with placebo versus 63% with sorafenib (P = .382); median OS had not yet been reached.[2]

Of note, in 46 FMS-like tyrosine kinase 3 (FLT3)-internal tandem duplication (ITD)-positive patients, no difference in EFS was observed; however, there was a trend toward a prolonged RFS and OS in favor of sorafenib. A possible explanation for the beneficial, nonspecific effects of sorafenib includes its effect on multiple kinases, such as vascular endothelial growth factor, platelet-derived growth factor, c-Kit, Raf kinases, and others.[2]

Intensification of DA in Induction in AML

Data were also presented from the first randomized trial of 90 mg/m^2 of DA versus 60 mg/m^2 of DA in AML.[3] Recent evidence has suggested improved rates of remission and OS from intensification of DA in induction with a higher dosage (90 mg/m^2) versus the standard dosage (45 mg/m^2) for patients with AML 17 to 65 years.[4,5]

The UK NCRI AML17 trial randomized 1206 patients (median age 53 years; range, 16-72 years) with AML in a 1:1 fashion to 90 mg/m^2 or 60 mg/m^2 of DA on days 1, 3, and 5 in their first induction course, followed by 50 mg/m^2 on days 1, 3, and 5 in their second course. No differences in remission rate were demonstrated, as remission was achieved in 81% of patients in the 90-mg/m^2 cohort and 84% of patients in the 60-mg/m^2 cohort (odds ratio [OR] 1.21, 0.90-1.64; P = .1). Two-year RFS was 52% versus 50% in the 90-mg and 60-mg arms, respectively (hazard ratio [HR] 1.06, 0.85-1.32; P = .6), and cumulative incidence of relapse was 37% in the 90-mg arm versus 41% in the 60-mg arm (HR = 1.01, 0.79-1.30; P = .9). Two-year OS was

59% versus 60% in the 90-mg and 60-mg arms, respectively (HR = 1.17, 0.95-1.44; *P* = .14), suggesting that the lower dose could be adopted without negatively affecting outcomes. Finally, subgroup analyses including age, karyotype, performance status, and FLT3-ITD/NPM1 genotypes did not show any benefit for the 90-mg dosage versus the 60-mg dosage.[3]

Azacitidine Versus Conventional Care Regimens

A large phase 3 multicenter randomized trial, the AZA-AML-001 study, demonstrated that compared with conventional care regimens (CCR), treatment with azacitidine (AZA) prolonged median OS by approximately 4 months (10.4 months vs 6.5 months; *P* = .1009) in older patients with newly diagnosed AML. Patients with AML with morphologic dysplastic changes (AML-MDC) comprised about 33% of participants in the trial.[6]

An international team of researchers sought to determine the effects of AZA versus CCR on OS, response, and safety in the subset of patients with AML-MDC in the AZA-AML-001 trial (n = 158), and to further analyze OS in patients with AML-MDC who had been preselected to receive low-dose cytarabine (LDAC) before randomization to AZA or CCR. The investigators found that the median OS in patients with AML-MDC was doubled with AZA versus CCR, 12.7 months versus 6.3 months, respectively (95% CI, 7.2-14.1; HR = 0.69, 0.48-0.98; *P* = .0357). One-year survival was also improved with AZA versus CCR, at 50.7% versus 33.8%, respectively (16.9% difference; 95% CI, 1.5-32.2). Rates of CR plus complete remissions with incomplete blood count recovery were 26.7% with AZA versus 19.3% with CCR. The investigators concluded that AZA was safe, effective, and well tolerated in this high-risk subset of patients with AML compared with CCR, which is frequently used in this setting.[6] It will be interesting to see if AZA will replace LDAC in Europe following this trial.

Novel IDH2 Inhibitor

Early-stage testing of a novel inhibitor of the *IDH2* gene has shown promise in the treatment of leukemia and other hematologic blood cancers. *IDH2* is an enzyme that converts isocitrate to a-ketoglutarate. *IDH2* mutations cause decreased formation of a-ketoglutarate and increased formation of 2-hydroxyl glutarate, which acts as an oncometabolite by inducing epigenetic changes and impaired cell differentiation. AG-221 is a first-in-class, oral, potent, reversible, selective inhibitor of the *IDH2* mutant enzyme.[7] At ASH 2014, data were presented from an ongoing phase 1, open-label, dose-escalation study of AG-221. Patients with advanced *IDH2* mutation-positive hematologic malignancies were administered AG-221 as a single agent once or twice daily in 28-day cycles. The study's primary objectives were to determine the maximum tolerated dose (MTD) and safety, and to select a dosage and schedule for expansion cohorts and future phase 2 trials. Secondary objectives included assessment of clinical activity by investigators using the International Working Group Criteria, pharmacokinetics, and pharmacodynamics.[8]

Forty-eight patients have been enrolled since September 2013; 27 remain on treatment. To date, AG-221 has been well tolerated, with MTD not yet reached, and the majority of reported AEs were grade 1 or 2. Nine patients have died, 8 within the first 28 days of receiving AG-221. One patient with severe pneumonia also died, with the death reported as possibly being related to the drug. Eleven serious AEs in 8 patients were reported as possibly drug related.[8]

Investigator-assessed objective responses have been observed in 20 patients. Responses have been durable, including complete remissions of up to 4.5 months. Although still early, these data suggest that mutant *IDH2* is a valid therapeutic target.[8]

Fitness Criteria to Guide Treatment in Elderly With AML

The use of intensive chemotherapy, nonintensive chemotherapy, or best supportive care to treat elderly patients with AML is a subject of ongoing debate. Although treatment choice is largely driven by a patient's age, the role of fitness and comorbidities in treatment choice and outcome has garnered increasing attention in recent years.[9] In 2013, Ferrara and colleagues proposed a set of objective criteria for defining patients as "fit" or "unfit" for intensive chemotherapy.[10] In an effort to validate these criteria in the clinical setting, a team of Italian physicians utilized these criteria to perform a retrospective analysis of a population-based series of patients with AML.[9]

Borlenghi and colleagues evaluated 350 patients 65 years or older who were diagnosed with AML at various hematologic centers in Italy between January 2008 and May 2014; median age was 73 years. Using Ferrara's criteria, the patients were classified as fit for intensive chemotherapy (fit), unfit for intensive chemotherapy (unfit), or unfit for nonintensive chemotherapy (frail).[9]

Of the 350 evaluable patients, 170 (46.9%) were classified as fit, 140 (38.7%) were classified as unfit, and 40 (11%) were classified as frail. Median OS of fit, unfit, and frail patients was 12.5 months, 3.7 months, and 1.8 months, respectively (fit vs others, *P* =. 0001; unfit vs frail, *P* =.049). Overall concordance between Ferrara's fitness criteria and the treatment actually received by the patients was 80% (71% in fit, 88% in unfit, and 90% in frail patients).[9]

In this analysis, fitness level was significantly related to survival. The median OS of patients receiving intensive chemotherapy, nonintensive chemotherapy, or best supportive care was 14.7 months, 14.2 months, and 4.2 months, respectively, in fit patients (*P* <.0001), and 8.6 months, 8.9 months, and 2 months, respectively, in unfit patients (*P* <.0001). Median OS in frail patients receiving nonintensive chemotherapy (n = 4) or best supportive care was 11.5 months and 2 months, respectively (not significant). The authors concluded that Ferrara's fitness criteria appear to be useful for identifying patients likely to benefit from

intensive or nonintensive chemotherapy as opposed to best supportive care, and for making decisions when treating elderly patients with AML.[9] A prospective study is needed to substantiate these findings.

Quizartinib in AML

FLT3-ITD mutations have been associated with early relapse and poor survival in AML. The novel agent quizartinib (formerly AC220) is a potent, targeted FTL3 inhibitor that selectively inhibits FLT3 kinase activity. Gautem Borthakur, MD, and colleagues from MD Anderson Cancer Center in Houston presented data from a planned interim analysis of an ongoing phase 1/2 trial testing whether the addition of quizartinib to salvage therapy with AZA or LDAC will improve response rates versus monotherapy with either agent. The primary objective of the phase 1 trial was to determine the dose-limiting toxicity and MTD of the combination of quizartinib with either AZA or LDAC; the objective of the phase 2 trial was to determine the clinical activity of both combinations.[11]

At present, 26 patients have been enrolled, 18 to the AZA arm and 8 to the LDAC arm. Quizartinib 60 mg/day was selected as the recommended phase 2 dosage based on emerging results from a separate dose-finding study. Eighteen patients, all with *FLT3-ITD* mutations without *D835* mutations, have responded, including 5 patients (63%) in the LDAC arm and 13 patients (72%) in the AZA arm. The overall response rate was 82% among patients with *FLT3-ITD* mutations (n = 22). These rates were higher than what was expected with either agent alone. Patients continue to be enrolled to both arms of the trial.[11]

CAR-T Cells

Some of the most exciting and interesting early-stage developments concern the use of chimeric antigen receptor-modified T cells (CAR-T cells), which have demonstrated increasing potential for the treatment of various hematologic malignancies. Preclinical and clinical studies utilizing this type of adoptive immunotherapy have achieved dramatic successes in the treatment of AML, chronic lymphocytic leukemia (CLL), and solid tumor cancers, spurring ongoing investigations.[12] By engineering T-cell function, as well as creating vigorous anti-tumor T-cell response and cancer-targeting memory T cells, it is hoped that this novel therapeutic approach may offer long-term disease control and possibly even curative potential.[12]

Much of the current research in CAR-T cells is focused on identifying suitable antigen target cells that produce potent anticancer effects while minimizing toxicity.[12] Carl H. June, MD, of the Abramson Cancer Center, University of Pennsylvania Perelman School of Medicine in Philadelphia, presented data at ASH highlighting the current status of trials testing CAR-T cell therapy for relapsed or refractory acute lymphoblastic leukemia (ALL), CLL, AML, and for myeloma, including very encouraging survival data (**Table**).[13]

June reported that as of April 2014, 25 children and 5 adults with relapsed or refractory ALL were treated with CTL019, the most developmentally advanced CAR-T cell therapy, which was granted breakthrough therapy status by the FDA in July 2014. Remarkably, complete remissions were achieved in 90% of patients (27/30), and sustained remissions were achieved in 15 of 22 evaluable patients, with median follow up of 7 months. The rate of EFS was 67% (95% CI, 51%-88%), and OS was 78% (95% CI, 65%-95%) at 6 months.[13]

To date, more than 50 patients with advanced refractory CLL have been treated with CTL019. Two of the first 3 patients treated remain in complete remission nearly 4 years after infusion. Phase 2 and 3 trials are needed to further establish the efficacy and safety of this promising therapy.[13] The reason(s) for different response rates between ALL and CLL is unclear at this point.

Data presented by Kochenderfer and colleagues suggest that anti-CD19 CAR-T cells administered following low-dose chemotherapy may induce remission in patients with chemotherapy-refractory large B-cell lymphoma and may also reduce the overall toxicity of the therapy. The investigators treated 9 patients with B-cell lymphoma with a single infusion of anti-CD19 CAR-expressing T cells that was preceded by a low-dose chemotherapy

TABLE. CD19-Targeted Chimeric Antigen Receptor T-Cell Therapy for B-ALL

	Number of Patients	Construct	CR (%)	MRD Negativity (%)	Relapse-Free Survival (%)	Follow-Up (months)
Park	24	Retroviral, 19-28z	90[a]	90	N/A[a]	N/A
Grupp	30	Lentiviral, CD19-BB-z	90	73	67	6
Lee	20	Retroviral, FMC63-28z	70	60	79	4.8

CR indicates complete remission; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease; N/A, not available.
[a]7 of 10 eligible patients proceeded to allogeneic HSCT without evidence of relapse.

regimen administered daily for 3 days (cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2). Eight of the 9 treated patients had diffuse large B-cell lymphoma that was refractory to or that had relapsed less than 1 year after autologous stem cell transplantation—grim clinical scenarios with a median OS of less than 1 year.[14]

Despite their poor prognoses, 1 patient obtained a CR and 4 obtained partial responses, including resolution of large lymphoma masses in some cases. Compared with previous studies that utilized high-dose chemotherapy prior to administration of anti-CD19 CAR-T cells, toxicity was reduced when CAR-T cells were infused after low-dose chemotherapy. There were no cases requiring vasopressor drugs or mechanical ventilation, and cytopenias were mild.[14]

Blinatumomab in ALL

The detection of leukemic cells in bone marrow by polymerase chain reaction or flow cytometry in the presence of hematologic CR in ALL is known as minimal residual disease (MRD). Patients with persistent or recurrent MRD after induction therapy are known to have a greater risk of relapse than those with no detectable MRD. When patients have MRD, the goal of treatment is to avoid hematologic relapse, reduce MRD load, and provide a bridge to subsequent hematopoietic stem cell transplantation (HSCT).[15]

Blinatumomab is an investigational bi-specific T-cell (BiTE) antibody construct that redirects CD3 T cells to CD19 target cells, resulting in serial lysis of CD19 B cells. In a phase 2 study of first-line blinatumomab in patients with MRD ALL (n = 21), 80% of evaluable patients achieved a complete MRD response.[16] That trial was followed by BLAST, a confirmatory, single-arm, phase 2 study that evaluated the efficacy, safety, and tolerability of blinatumomab in patients with MRD ALL, the results of which were presented at ASH.[15]

BLAST enrolled patients 18 years or older with B-precursor ALL in hematologic CR (<5% blasts in bone marrow) after 3 or more intensive chemotherapy treatments and with MRD ≥10. Blinatumomab 15 µg/m^2/day was administered for 4 weeks by continuous IV infusion, followed by a 2-week treatment-free period (1 cycle). Responders could receive up to 4 cycles of treatment or undergo HSCT after at least 1 cycle. Patients who experienced hematologic relapse discontinued treatment. The primary endpoint was rate of complete MRD response; OS, RFS, duration of complete MRD response, and incidence and severity of AEs were secondary endpoints. OS and RFS will be analyzed after a minimum of 18 months of follow up.[15]

The trial enrolled 116 patients, each of whom received treatment. Median age was 45 years; 13% (15) patients were aged ≥65 years. As of February 2014, 74 patients had completed treatment (4 cycles or 1 cycle followed by HSCT) and 32 patients had discontinued treatment due to AEs, disease relapse, or investigator decision; an additional 79 patients were still alive and being followed. Three patients were excluded from the efficacy analysis: 1 patient had no central lab assay and 2 patients had assays with a sensitivity of 5×10^{-4}.[15]

Among evaluable patients, 78% (88) had a complete MRD response following 1 cycle (95% CI, 69%-85%), confirming that the study met its primary objective. Two additional patients had a complete MRD response after more than 1 cycle of blinatumomab. The complete MRD response rate across all cycles was 80%. All patients experienced at least 1 AE. The most common AEs, occurring in ≥20% of patients, included pyrexia (88%), headache (38%), tremor (29%), chills (25%), fatigue (24%), nausea (22%), and vomiting (22%). Sixty percent of patients experienced serious AEs: 59% and 27% of patients had grade ≥3 and grade ≥4 AEs, respectively. Serious AEs occurring in ≥5% of patients were pyrexia (15%), tremor (7%), aphasia (5%), encephalopathy (5%), and overdose (5%). Two fatal AEs occurred on treatment, 1 of which (atypical pneumonia) was considered treatment-related. These results suggest that blinatumomab may have the potential to effectively eradicate MRD following intensive treatment.[15] A large study of blinatumomab in relapsed/refractory CD19-positive ALL was recently published in *Lancet Oncology*[17] and blinatumomab was recently approved by the FDA for relapsed/refractory ALL.

Adolescents and Young Adults (AYA) with ALL

Retrospective analyses have shown that AYA with ALL have significantly improved survival when treated according to pediatric versus adult regimens. As such, the large, prospective C10403 US intergroup trial sought to evaluate the feasibility and effectiveness of treating AYA ALL patients (aged 16-39 years) using the Capizzi methotrexate arm of the successful Children's Oncology Group regimen (COG AALL0232). EFS was the primary endpoint.[18]

AYA patients with newly diagnosed B-precursor ALL (B-ALL) or T-precursor ALL (T-ALL) were enrolled in the trial. The treatment protocol consisted of 5 intensive courses: remission induction, remission consolidation, interim maintenance, delayed intensification, and prolonged maintenance therapy. Patients with M2 marrow response (>5% but <25% lymphoblasts) after remission induction received an extended remission induction course of therapy.[18]

From November 2007 through August 2012, 318 patients with a median age at diagnosis of 24 years were enrolled in the study; 22 patients withdrew prior to therapy. The majority of evaluable patients had B-ALL and were male (76% and 61%, respectively).[18] Five deaths occurred that were deemed treatment-related: these included liver failure in 2 patients, both during induction; infection in 1 patient during induction and 1 in consolidation; and ventricular arrhythmia in 1 patient during induction. Treatment toxicities were similar to those reported in the Capizzi metho-

trexate arm of COG AALL0232, with an increased incidence of thrombosis and early hyperbilirubinemia.[18]

To date, 87 patients remain on treatment and 70 patients have died. The median EFS is 59.4 months (95% CI, 38.4 - not reached), and the 2-year EFS rate is 66% (95% CI, 60%-72%). Similar 2-year EFS rates were observed in B-ALL patients and T-ALL patients (65% and 68%, respectively). The 2-yr OS rate was 78% among B-ALL patients (95% CI, 72%-83%) and 80% for T-ALL (95% CI, 72%-84%).[18]

The investigators noted that the absence of detectable MRD was associated with 100% EFS (P = .0006). The improvements in clinical outcomes demonstrated in this trial are expected to form the basis for future trials, including those using novel agents to further improve survival for AYA with ALL.[18] Another unique finding of this trial is the characterization of Philadelphia (Ph)-chromosome-like phenotype in 28% of the patients; their EFS was a mere 52% compared with 82% (P = .04) in patients without this phenotype. Novel approaches for Ph-like ALL are urgently needed.

Nilotinib + Chemotherapy for Ph+ ALL

The prognosis of elderly patients with Ph+ ALL has remained poor in spite of the high complete hematologic remission (CHR) rates achieved with imatinib-based treatment, largely due to the tendency to relapse in that patient subset. The potent ABL tyrosine kinase inhibitor (TKI) nilotinib has been approved for the treatment of chronic and accelerated phase CML, but limited data on its efficacy in Ph+ ALL are available. To study the activity of an ABL-TKI regimen in the front-line setting, the European Working Group for Adult ALL developed a joint chemotherapeutic protocol for first-line therapy of elderly Ph+ ALL patients.[19]

Patients 55 years or older with Ph+ and/or *BCR-ABL1*-positive ALL were enrolled in the trial. The only prior treatments that were permitted were corticosteroids, single-dose vincristine, or 3 doses of cyclophosphamide. The trial's primary endpoint was the rate of patients without an event at 12 months (an event was defined as relapse, death, serious AE, or treatment discontinuation). Secondary endpoints included EFS, OS, the rate of CHR after induction; death during induction or in CHR; and the rate of major molecular response or complete molecular response defined by *BCRABL1/ABL1* ratios <0.1% and < 0.001%, respectively.[19]

As of August 2014, 47 patients with a median age of 66 years were enrolled. The CHR rate among patients evaluable for response (36) was 97%; 1 patient was refractory (3%). No patient died during induction therapy. After a median follow up of 211 days, 31 of 35 evaluable patients were in complete cytogenetic response and 4 patients had relapsed, 2 of whom had discontinued study treatment in order to undergo allogeneic stem cell transplant. Eight of 35 CR patients completed the consolidation cycles and have entered maintenance phase; 5 patients have completed protocol therapy. The rate of complete molecular remission after induction was 30%, and 2 patients had undetectable *BCR-ABL1* transcripts. During the consolidation phase, 42% of patients had a complete molecular remission, and *BCR-ABL1* transcripts were undetectable in 29% of patients.

Tolerability was acceptable, with 34 serious AEs reported to date: 11 during induction, 16 during consolidation, 6 during the maintenance phase, and 1 following study discontinuation. Infectious events and neutropenic fever were the most common AEs. The investigators concluded that nilotinib combined with chemotherapy was well tolerated and highly effective, with a 97% CR in elderly patients with newly diagnosed Ph+ ALL. Molecular response rates were high, and MRD levels in responding patients have continued to decrease. This abstract suggests that nilotinib can become part of the armamentarium for Ph+ ALL.

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Disclosures: Dr Wetzler serves as a consultant to Novartis, Sigma-Tau, and Jazz Pharmaceuticals and is a principal investigator on studies with Bristol-Myers Squibb and Teva. Writing assistance was provided by Kathleen Krafton, a freelance medical writer for *AJHO*. Ms Krafton has no relevant financial conflicts of interest to disclose.

Acknowledgment of support: Supported partially by grants from the National Cancer Institute Grant CA16056, the Szefel Foundation, Roswell Park Cancer Institute, the Leonard S. Lu-Vullo Endowment for Leukemia Research, the Nancy C. Cully Endowment for Leukemia Research, the Babcock Family Endowment, and the Heidi Leukemia Research Fund, Buffalo, NY.

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