American Society of Hematology
Annual Meeting and Exposition

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Billed as the world’s premier event in malignant and nonmalignant hematology, this year’s American Society of Hematology (ASH) meeting hosted more than 27,000 hematology professionals December 3–6 in San Diego. We review below key sessions on pharmacotherapy clinical trials across a wide span of disease states, including leukemia, graft-versus-host disease, myelofibrosis, multiple myeloma, and sickle cell disease.

Minimal Residual Disease Negative Complete Remissions Following Anti-CD22 Chimeric Antigen Receptor Therapy in Children and Young Adults with Relapsed/Refractory Acute Lymphoblastic Leukemia

• Terry J. Fry, MD, National Cancer Institute, Bethesda, Maryland

A National Cancer Institute (NCI) phase 1 study of anti-CD22 chimeric antigen receptor (CAR) therapy in children and young adults with relapsed/refractory acute lymphoblastic leukemia (ALL) revealed complete remissions without severe or irreversible neurotoxicity.

Not all relapsed/refractory ALL patients respond to anti-CD19 CAR therapy, and CD19-negative escape has been observed, Dr. Fry said at an ASH press briefing. He noted that CD22, which is widely expressed in ALL, represents an ideal target. The NCI trial tested anti-CD22 CAR therapy to determine the feasibility of producing anti-CD22 CAR cells and the safety of administering escalating doses of anti-CD22 CAR T cells. Preliminary assessment of antileukemia effects, a secondary endpoint, was also conducted.

Anti-CD22 CAR T-cell therapy, in which a patient’s own genetically altered T cells track down and kill cancer cells expressing CD22, plus fludarabine 25 mg/m² was given to 16 patients 1 to 30 years of age with relapsed/refractory CD22-positive hematologic malignancies. All patients had CD22 expression on more than 99% of their malignancy, with a median site density of 2,589 molecules per cell (range, 846–13,452). All had previously undergone at least one allogeneic stem cell transplant, and a majority of participants (11 of 16) had relapsed after receiving anti-CD19 CAR T-cell therapy before entering the trial.

Among the 10 participants treated at a higher dose (comparable to that used by current CD19 CAR programs), eight attained a complete remission without evidence of residual disease after one month of their infusion. Two patients had mild cytokine release syndrome. Three patients are in ongoing sustained remission with durations of more than one year, six months, and three months.

Relapses were associated with changes in CD22 expression level. “We’ve been able to show that you can give a second CAR therapy that is directed against a different antigen and have it be safe and effective,” Dr. Fry said, noting that a single antigen-directed CAR immunotherapy probably won’t be sufficient for long-term durable remissions in many patients. The potential for targeting multiple cancer-related proteins (also called bispecific targeting) is suggested by this feature, he said.

“This is the first successful salvage CAR therapy for CD19-negative B-ALL,” he concluded.

Chronic Myeloid Leukemia Patients With Stable Molecular Responses May Safely Decrease the Dose of Their Tyrosine Kinase Inhibitor: Data from the British DESTINY Study

• Mhairi Copland, MD, PhD, University of Glasgow, Glasgow, United Kingdom

Like patients with deep molecular responses, most chronic myeloid leukemia (CML) patients with stable responses (molecular response with a 3.0 log reduction [MR3]; BCR–ABL protein level less than 0.1%) can safely cut their tyrosine kinase inhibitor (TKI) dose in half. The consequence, according to Dr. Copland, is fewer side effects and reduced cost.

Reporting findings from the DESTINY study at an ASH press briefing, Dr. Copland noted that several studies report 50% to 60% of CML patients with enduring good responses can stop TKI therapy. All of these studies, however, are restricted to patients with very deep responses (less than MR4; BCR–ABL less than 0.01%). Dr. Copland asked, “What about patients with less deep responses? … Could they manage on reduced-dose treatment? This might improve side effects and save money.”

One of the challenges in CML, she added, is how to manage patients with side effects.

DESTINY included CML patients in MR4 or better and in MR3. They were assigned half-dose therapy with imatinib (Gleevec, Novartis) 200 mg once daily (n = 148), nilotinib (Tasigna, Novartis) 200 mg twice daily (n = 16), or dasatinib (Sprycel, Bristol-Myers Squibb) 50 mg once daily (n = 10).

Individual TKI side effects such as lethargy, diarrhea, rash, nausea, periorbital edema, and hair thinning improved in the first one to two months of de-escalation, but plateaued thereafter. Quality-of-life measures were optimal at the trial outset, however, and were not impacted.

Molecular relapses, defined as loss of MR3 on two consecutive samples, were reported for 12 patients between study months 2 and 12. The molecular relapse rate was higher in patients with less deep molecular responses at the outset (MR4 in three of 125 patients [2.4%]; MR3 in nine of 49 patients [18.4%]).

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According to Dr. Copland, halving treatment led to a 46.7% cost savings of £1,943,364 (US $1,530,204) from an expected TKI budget (without de-escalation) of £4,156,969 (US $3,273,197). “In CML patients with stable MR3 or better, decreasing TKI treatment to half the standard dose appears safe and is associated with improvement in TKI-related side effects, implying that many patients with stable responses are being overtreated,” Dr. Copland concluded. “Studies of more ambitious de-escalation are warranted.”

**Cessation of Tyrosine Kinase Inhibitor Treatment in Chronic Myeloid Leukemia Patients with Deep Molecular Response: Results of the EURO-SKI Trial**

• Francois-Xavier Mahon, MD, PhD, University of Bordeaux, Bordeaux, France

In a clinical trial with a large cohort of chronic myeloid leukemia (CML) patients, stopping tyrosine kinase inhibitor (TKI) therapy was feasible and safe, according to findings from the EURO-SKI trial, which were discussed by Dr. Mahon in an ASH press briefing.

The feasibility of stopping TKI treatment has been demonstrated previously, and the concept of treatment-free remission was validated in the STIM study. While it has been established that a sustained deep molecular remission on long-term TKI therapy is necessary prior to an attempt at treatment-free remission, the exact preconditions for stopping CML treatments are not defined.

The EURO-SKI trial included 821 patients treated at 61 sites in 11 countries. All were chronic-phase CML patients who had received imatinib (Gleevec, Novartis), nilotinib (Tasigna, Novartis), or dasatinib (Sprycel, Bristol-Myers Squibb) for three years or more without treatment failure. All were in deep molecular response (molecular response with a 4.0 log reduction [MR4]; BCR–ABL protein level less than 0.01% on the international scale) for at least one year.

Molecular recurrence in the EURO-SKI study was defined by the loss of the major molecular response (BCR–ABL less than 0.1% on the international scale) at any point. Loss of major molecular response among the 755 evaluable patients occurred in 373 patients. That loss occurred within the first six months in 78.3% of patients (n = 292). Median follow-up was 14.9 months for the entire group and 26.0 months among the 383 patients who did not experience loss of response. Molecular recurrence-free survival was 61% at six months, 52% at 18 months, and 47% at 36 months.

While gender, age, or any other variable did not predict the probability of successful therapy cessation, longer duration of imatinib therapy (optimally 5.8 years or longer) prior to TKI cessation correlated with a higher probability of relapse-free survival. In addition, each additional year of TKI therapy increased a patient’s chances of successful TKI discontinuation by about 16%. Resumption of TKI therapy for patients with molecular recurrence led to regaining prior remission levels in most patients, and none progressed to advanced disease.

With about half of the enrolled patients remaining in remission two years after stopping their TKI therapy, Dr. Mahon concluded, “With inclusion and relapse criteria less strict than in many previous trials, and with decentralized but standardized PCR [polymerase chain reaction] monitoring, stopping of TKI therapy in a large cohort of CML patients appears feasible and safe.”

**Multicenter, Open-Label, Phase 2 Study Of Ibrutinib in Chronic Graft-Versus-Host Disease After Failure of Corticosteroids**

• David Miklos, MD, Stanford University, Palo Alto, California

Data from a multicenter, open-label, phase 2 study of ibrutinib (Imbruvica, Pharmacyclics/Janssen) support the kinase inhibitor’s use in patients with steroid-refractory chronic graft-versus-host disease (GVHD). Dr. Miklos said in a late-breaking clinical trials session.

He described GVHD as a complication of allogeneic stem cell transplantation that affects approximately 4,000 of the 10,000 individuals in the United States who undergo allogeneic stem cell transplantation each year. Immune-suppressing corticosteroids, the standard treatment, do not benefit all patients. The kinase inhibitor ibrutinib, which was recently granted breakthrough therapy status by the Food and Drug Administration, reduces the severity of chronic GVHD through its inhibition of Bruton tyrosine kinase and interleukin-2–inducible T-cell kinase. Both B and T cells play a role in the pathophysiology of chronic GVHD, Dr. Miklos said.

All 42 patients (median age, 56 years; range, 19–74 years) with chronic GVHD in Dr. Miklos’ study needed additional therapy. Included patients had received prior regimens for chronic GVHD and had erythematous rash over more than 25% of their body surface or National Institutes of Health mouth scores of greater than 4. All were treated daily with 420 mg ibrutinib until unacceptable toxicity or disease progression. The study evaluated the efficacy and safety of ibrutinib, with changes in corticosteroid use among the secondary endpoints.

Median duration of chronic GVHD was 13.7 months at study entry. The median number of prior regimens was two (range, one to three). The overall response rate, after a median follow-up of 13.9 months, was 67%. Complete responses were observed in 45% of patients, with sustained responses of 20 weeks or greater in 71% and 32 weeks or greater in 48%.

Curtailed or reduced corticosteroid use was facilitated with ibrutinib, with low corticosteroid doses (less than 0.14 mg/kg per day) given in 75% of patients and complete cessation of corticosteroid use while in response in five patients (12%). Clinician-assessed chronic GVHD median severity scores decreased from 7 at baseline to 4 at week 49. Score improvements using the Lee chronic GVHD symptom scale were reported overall in 61% of the 28 responders versus 11% in nine nonresponders.

Adverse events, consistent with those previously observed for ibrutinib in B-cell malignancies and chronic GVHD, were experienced in 45% of patients. The most common adverse events were fatigue (57%), diarrhea (36%), muscle spasms (29%), nausea (26%), and bruising (24%). Two fatal events (multilobular pneumonia and bronchopulmonary aspergillosis) were reported.
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Dr. Miklos underscored the importance of active monitoring to manage ibrutinib-related adverse events. He commented that analysis of biomarker changes shows that ibrutinib has a positive effect on immune cell subsets.

“I think clinicians will find these data support the use of ibrutinib in patients with steroid-refractory chronic GVHD,” Dr. Miklos concluded.

Results of the PERSIST-2 Phase 3 Study of Pacritinib Versus Best Available Therapy, Including Ruxolitinib, In Patients With Myelofibrosis and Platelet Counts Less Than 100,000 per mcL

* John Mascarenhas, MD, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, New York

Among patients with myelofibrosis (MF) and platelet counts of less than 100,000 per mcL, pacritinib was significantly more effective than the best available therapy (BAT) (including ruxolitinib [Jakafi, Incyte]) for spleen volume reduction. A trend toward improved total symptom score was also observed, according to an ASH late-breaking clinical trial presentation by Dr. Mascarenhas.

A life-threatening hematologic malignancy characterized by splenomegaly and debilitating constitutional symptoms, MF presents with thrombocytopenia, platelet counts of less than 50,000 per mcL (associated with reduced quality of life), heavier symptom burden, and likelihood of shortened overall survival in 25% of patients. The Janus kinase 1 (JAK1)/JAK2 inhibitor ruxolitinib has been shown to reduce splenomegaly and related symptoms. However, it is associated with dose-limiting cytopenias and is not indicated for patients with platelet counts of less than 50,000 per mcL. Pacritinib is an oral kinase inhibitor with specificity for JAK2, FMS-like tyrosine kinase-3, interleukin-1 receptor-associated kinase 1, and colony-stimulating factor 1 receptors.

In the PERSIST-1 trial, which compared pacritinib to BAT (excluding JAK2 inhibitors), pacritinib demonstrated sustained spleen volume reduction and symptom control in MF patients regardless of baseline platelet counts. The PERSIST-2 phase 3 trial tested two doses of pacritinib (400 mg once daily [QD] and 200 mg twice daily [BID]) versus BAT (including ruxolitinib). The coprimary endpoints were the number of patients achieving spleen volume reductions of 35% or greater and reductions in total symptom score of 50% or greater at week 24. The 1:1:1 randomization included 75 patients receiving pacritinib QD, 74 receiving pacritinib BID, and 72 receiving BAT. Mean age was approximately 68 years, and 57% of the patients were men. Median spleen length was approximately 14 cm. Approximately 44% of patients had received prior treatment with ruxolitinib. BAT most commonly consisted of ruxolitinib (45%) and hydroxyurea (19%). The safety and overall survival analysis included approximately 100 patients per arm.

The PERSIST-2 study was truncated by a Food and Drug Administration (FDA)-mandated full clinical hold ordered after interim analysis revealed patient deaths related to intracranial hemorrhage, cardiac arrest, and heart failure. At the time of the clinical hold, there had been 15 deaths in the QD arm (14%), 10 deaths in the BID arm (9%), and 14 deaths (14%) in the BAT arm. The rates for the primary endpoint of spleen volume reduction at 24 weeks were significantly improved for both pacritinib arms versus BAT (QD, 14.7%, \( P = 0.017 \); BID, 21.6%, \( P = 0.001 \)). Percentages of patients with 50% or greater total symptom score reductions were significantly higher only for the pacritinib BID arm versus BAT (32.4% versus 13.9%, \( P = 0.011 \)).

Overall survival was censored at the clinical hold date. It was slightly higher with pacritinib versus BAT in the QD group (hazard ratio [HR] = 1.18) but was lower in the BID group (HR = 0.68). The need for red blood cell transfusions at week 24 was reduced in the pacritinib arms, especially the BID arm (0.67 units per month versus 1.33 in the BAT arm).

Serious cardiac events and bleeding events were comparable among all groups and were relatively rare. The most common adverse events with pacritinib were diarrhea, vomiting, nausea, anemia, and low platelet count.

“Despite study truncation due to the clinical hold, pacritinib QD and BID was significantly more effective than best available therapy, including ruxolitinib, for spleen volume reduction with a trend toward improved total symptom score,” Dr. Mascarenhas said. He also noted that the pacritinib BID benefit-risk profile appeared to be better than that of BAT, including ruxolitinib.

The FDA recommended that the manufacturer conduct dose-exploration studies for pacritinib in patients with MF and should submit final study reports and datasets for PERSIST-1 and PERSIST-2.

**SUSTAIN: A Multicenter, Randomized, Placebo-Controlled, Double-Blind, 12-Month Study to Assess Safety and Efficacy of SEG101 With or Without Hydroxyurea Therapy in Sickle Cell Disea Patients With Sickle Cell–Related Pain Crises**

* Kenneth I. Ataga, MD, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

High-dose SEG101 (crizanlizumab, formerly SelG1, Novartis) resulted in a statistically significant and clinically meaningful reduction in the frequency of sickle cell–related pain crises (SCPCs) in patients with sickle cell disease, according to SUSTAIN clinical trial results presented at an ASH press briefing. SEG101 is a first-in-class humanized anti-P-selectin antibody given as an intravenous infusion over 30 minutes. Upregulation of P-selectin, an adhesion molecule expressed on activated vascular endothelial cells and platelets, plays a key role in the pathogenesis of SCPC, Dr. Ataga said.

In sickle cell disease, pain is caused by tissue ischemia created when sickled red blood cells and leukocytes adhere to the endothelium and lead to vaso-occlusion. SCPCs occur unpredictably and often require hospitalization, Dr. Ataga explained. While hydroxyurea is known to decrease SCPC frequency in sickle cell anemia, many patients receiving hydroxyurea continue to experience acute painful episodes.
In SUSTAIN, investigators randomized sickle cell patients double-blind to placebo (n = 65), SEG101 2.5 mg/kg (n = 66), or SEG101 5.0 mg/kg (n = 67). Patients received an initial dose, one dose 14 days later, and then one dose every four weeks through week 50 for a total of 14 doses. The primary efficacy endpoint was the annual rate of SCPC in the 5.0-mg/kg SEG101 group versus placebo. An SCPC was defined as acute sickle cell–related pain that resulted in a visit to a medical facility and required a parenteral or oral narcotic or parenteral nonsteroidal anti-inflammatory drug. The primary endpoint was the median rate of SCPC per year.

Median patient age was 28 years, 45% of patients were male, and approximately 93% were African-American. Concomitant hydroxyurea was being taken by 62% of patients.

For patients receiving the higher SEG101 dose, the median rate of SCPC per year was 1.63. For those receiving the lower dose, it was 2.01, and for patients receiving placebo, it was 2.98. In the high-dose group, 24 patients were SCPC-free. Twelve in the low-dose SEG101 group were SCPC-free over the course of the study, as were 12 in the low-dose group and 11 in the placebo group. Median time to the first and second SCPC events was significantly longer in the high-dose SEG101 group (4.07 months and 10.32 months, respectively; P = 0.001) than in the placebo group (1.38 months and 5.09 months, respectively; P = 0.022). Differences between the low-dose SEG101 group and placebo group were not significant. Adverse event incidence with SEG101 was low.

“Treatment with high-dose SelG1 [SEG101] resulted in a statistically significant and clinically meaningful reduction in the frequency of SCPC in patients with sickle cell disease,” Dr. Ataga concluded.

A Phase 1b Study of Vadastuximab Talirine In Combination With 7+3 Induction Therapy For Patients With Newly Diagnosed Acute Myeloid Leukemia

• Harry P. Erba, MD, PhD, University of Alabama at Birmingham, Birmingham, Alabama

Vadastuximab talirine (VDT) can be safely combined with standard 7+3 chemotherapy in patients with newly diagnosed acute myeloid leukemia (AML), according to preliminary results of an ongoing phase 1b trial. Standard induction treatment for this population has been 7+3 (cytarabine for 7 days with an anthracycline for 3 days) for 30 years, Dr. Erba said in an ASH press briefing.

VDT is an antibody that targets the cell surface antigen CD33. CD33 is expressed in about 90% of AML and leads to cell death. Remissions brought about by adding VDT to 7+3 chemotherapy could be enhanced and deeper than those with standard chemotherapy alone, leading to minimal residual disease (MRD) status. “Achieving MRD-negative remission postinduction correlates with improved survival,” Dr. Erba said.

The safety and antileukemic activity of VDT added to the 7+3 regimen with induction on days 1 and 4 of a 28-day treatment cycle are being evaluated in Dr. Erba’s trial. The study includes 42 patients (36% male; mean age, 45.5 years) with previously untreated AML. Most patients have intermediate (50%) or adverse (36%) cytogenetic risk, and 17% of patients have secondary AML.

Adverse event rates with VDT are acceptable, according to Dr. Erba. Among hematologic treatment-related adverse events, grade 3 febrile neutropenia has been reported in approximately 65% of patients, and grade 4 thrombocytopenia, as expected, was reported in all patients. Nonhematologic toxicities were similar to those seen with 7+3 alone and most commonly included grades 1 and 2 nausea (60%), diarrhea (36%), and constipation (33%). No grade 3 or higher nonhematologic events have been observed in 15% or more of patients. The 30-day mortality rate is 2%. No veno-occlusive disease, sinusoidal obstruction syndrome, or significant hepatotoxicity has been observed.

Dr. Erba reported that complete remissions (CRs) have been achieved in 60% of patients, with 30 of 32 (94%) achieving CR within one cycle of therapy. Among these, 25 of 32 patients (78%) are MRD-negative. An additional 17% have CRs with incomplete platelet recovery. Dr. Erba observed that CRs tracked closely with cytogenic risk (favorable = 100%; intermediate = 67%; adverse = 40%).

“Vadastuximab talirine can be safely combined with 7+3,” Dr. Erba concluded, adding that the recommended dose is 20+10 mcg/kg on days 1 and 4. An alternate schedule of single-day dosing on day 1 is under investigation, and a randomized phase 2 trial of vadastuximab talirine plus 7+3 versus 7+3 alone is planned.

Survival Following Allogeneic Hematopoietic Cell Transplantation in Older High-Risk Acute Myeloid Leukemia Patients Initially Treated With CPX-351 Liposome Injection Versus Standard Cytarabine and Daunorubicin: Subgroup Analysis of a Large Phase 3 Trial

• Jeffrey E. Lancet, MD, Moffitt Cancer Center and Research Institute, Tampa, Florida

Treatment with CPX-351 for older patients with high-risk acute myeloid leukemia (AML) leads to better outcomes after allogeneic hematopoietic cell transplantation (HCT), according to an exploratory analysis of an open-label, parallel-arm study. This liposomal formulation of cytarabine and daunorubicin may also provide a bridge to successful transplant in poor-risk older AML patients, Dr. Lancet said in an ASH press conference.

Remission rates in patients older than 60 years of age are lower and induction mortality is higher compared with younger patients. CPX-351’s 5:1 molar ratio is said to maximize the synergy between cytarabine and daunorubicin, leading to preferential drug uptake into leukemic cells. In earlier phase 3 trial reporting, survival was superior in newly diagnosed older patients with secondary AML versus standard 7+3 cytarabine and daunorubicin.

Among older patients, Dr. Lancet observed, few can be cured with chemotherapy alone. He conducted an exploratory analysis among those patients who received allogeneic HCT after induction treatment. The study included patients 60 to 75 years of age with newly diagnosed secondary AML. Patients with complete responses (CRs) or CRs
with incomplete platelet or neutrophil recovery (CPX-351, n = 73; 7+3, n = 52) were considered for allogeneic HCT based on institutional criteria.

CRs (with and without platelet/neutrophil recovery) were more frequent with CPX-351 than with 7+3 (47.7% versus 33.3%). Also, median survival landmarked from time of transplant was not reached in the CPX-351 patients (n = 52) and was 10.25 months for the 7+3 patients (n = 39) (hazard ratio, 0.46, favoring CPX-351; \( P = 0.0046 \)).

While cautioning that the analysis is exploratory, Dr. Lancet underscored that the reduction in deaths was 53%, with all-cause mortality by day 100 after transplant at 9.6% in the CPX-351 group and 20.5% in the 7+3 group.

“Outcomes after allogeneic transplant in older patients with high-risk AML appear superior in patients treated with CPX-351,” he concluded. The findings of lower-induction–related morbidity and more patients in CR suggest that patients are transplanted in better condition, he commented.

REFERENCES


