European Hematology Association
The 19th Congress of the European Hematology Association (EHA) was attended by 10,827 physicians and other hematology researchers and professionals from June 12 to 15 in Milan, Italy. This report reviews key sessions on acute myeloid leukemia, chronic lymphocytic leukemia, β-thalassemia, multiple myeloma, and polycythemia vera, with a focus on new therapies (and one cost-effectiveness analysis).

Results of a Phase 3, Multicenter, Randomized, Open-Label Study of Azacitadine Versus Conventional Care Regimens in Older Patients With Newly Diagnosed Acute Myeloid Leukemia
- Hervé Dombret, MD, Professor of Hematology, Hôpital Saint Louis, University of Paris, Paris, France

In a study among patients with acute myeloid leukemia (AML), azacitadine compared with conventional care regimens (CCR) resulted in a clinically meaningful (P = 0.08) but not significant improvement in overall survival (OS). After censoring for subsequent AML therapy, however, the OS benefit was significant (P = 0.0147).

Older patients with AML have a poor prognosis, Dr. Dombret noted at a late-breaking clinical trial session, with median OS of only two to eight months, depending on their performance status, comorbidities, and biological risk factors (including cytogenetics). The therapeutic options for older AML patients worldwide are best supportive care (BSC), intensive chemotherapy (IC), and low-dose Ara-C (LDAC). He pointed out, however, that IC is not considered suitable for many older AML patients due to its high toxicity, particularly for those patients with significant comorbidities and more adverse risk factors. There have been no improvements in therapy in recent decades, he said.

An earlier randomized trial among older AML patients with 20% to 30% bone marrow blasts showed prolonged OS for azacitadine versus CCR. Dr. Dombret’s analysis compared the effects of azacitadine versus CCR on OS and on hematological response and safety in a large cohort of patients 65 years of age or older with newly diagnosed AML who had more than 30% bone marrow blasts in the international phase 3 AZA-AML001 study.

Included patients had Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, white blood counts of 15 x 10^9/L or lower, and intermediate- or poor-risk cytogenetics. All were ineligible for allogeneic stem cell transplant.

Two hundred and forty patients were preselected to receive one of three CCRs per investigator choice of best treatment:

- Conventional care regimen (CCR) resulted in a clinically meaningful (P = 0.08) but not significant improvement in overall survival (OS). After censoring for subsequent AML therapy, however, the OS benefit was significant (P = 0.0147).

Dr. Dombret noted no heterogeneity for OS, mortality, or safety in prespecified subgroups.

“After censoring, we have a significant gain with azacitadine in median overall survival—so that’s the first step. Next we have to find new agents for combinations that are tolerable and may prolong survival further,” Dr. Dombret concluded.

Ibrutinib Improves Survival in CLL and SLL Patients: Results From the RESONATE Study
- Peter Hillmen, MD, Professor of Experimental Hematology, Leeds Teaching Hospitals, St. James’s Institute of Oncology, Leeds, United Kingdom

Results of the phase 3 RESONATE trial reinforced and validated phase 2 trial data showing ibrutinib to be an effective new single-agent therapy for patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). “This will have a major impact for patients with refractory CLL,” Dr. Hillmen said in an interview.

The author is a freelance medical writer living in New York City.
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Patients with CLL or SLL who experience short response duration, are 65 years of age or older, or have adverse cytogenticities (i.e., deletion 17p) have poor outcomes and limited treatment options, he said in an EHA press briefing.

Ibrutinib is a first-in-class, once-daily oral covalent inhibitor of Bruton’s tyrosine kinase. In RESONATE, ibrutinib was compared with the anti-CD20 antibody ofatumumab in patients with relapsed or refractory CLL/SLL. Patients (N = 391) were randomized 1:1 to ibrutinib 420 mg until disease progression or unacceptable toxicity or to IV ofatumumab (300-mg initial dose followed by 11 doses of 2,000 mg).

An interim analysis conducted at a median of 9.4 months showed ibrutinib to significantly prolong progression-free survival (PFS). Median PFS for ofatumumab was 8.1 months and had not yet been reached with ibrutinib (HR, 0.215; 95% CI, 0.146–0.317; P < 0.0001). While median OS was not reached for either agent, the HR with ibrutinib compared with ofatumumab was 0.434 (95% CI, 0.238–0.789; P < 0.0049).

Dr. Hillmen said that the risk of progression or death with ibrutinib was 78% compared with ofatumumab, and 56% for death.

The impact of ibrutinib on PFS, OS, and overall response rate was observed irrespective of baseline clinical characteristics or molecular features, including high-risk del17p and purine-refractory subgroups. The improvements were both clinically and statistically significant, Dr. Hillmen commented, despite the crossover of 57 patients from ofatumumab treatment to ibrutinib after confirmed progression.

“These results encourage us to continue with our frontline studies of combination therapies,” Dr. Hillmen said. The findings, he said, should serve as confirmatory evidence required for Food and Drug Administration (FDA) accelerated approval. Ibrutinib was approved in November 2013 for mantle cell lymphoma and in February 2014 for CLL.

Interim Results From a Phase 2a, Open-Label, Dose-Finding Study to Determine the Safety, Efficacy, and Tolerability of Sotatercept (ACE-011) In Adults with β-Thalassemia

• John Porter, MD, Professor of Hematology, University College London, London, United Kingdom

ACE-536 Increases Hemoglobin Levels in Adults With β-Thalassemia: Preliminary Results from a Phase 2 Study

• Antonio Piga, MD, Professor of Medicine, University of Turin, Turin, Italy

Two phase 2 studies of novel, potential first-in-class activin receptor type IIA fusion proteins showed them to similarly increase hemoglobin and reduce transfusion burden in patients with β-thalassemia. Both agents are being developed by Acceleron (Cambridge, Massachusetts) in conjunction with Celgene (Summit, New Jersey). The intention, according to Acceleron Senior Vice President Steven Ertel, is to take the most promising agent into phase 3 trials.

Results for sotatercept, the first of the two similar agents, were presented in an oral session by Dr. Porter, who noted that the β-thalassemias are characterized by ineffective erythropoiesis leading to anemia and erythroid hyperplasia requiring transfusions. This, in turn, causes iron overload and organ failure, in particular fibrosis of the liver and the major cause of death, cardiac overload. He said also that sotatercept promotes late-stage red blood cell (RBC) precursor cell differentiation, increasing the release of mature erythrocytes into the circulation. Its mechanism is distinct from that of erythropoietin, which can worsen complications, Dr. Porter said. Both sotatercept and the other agent, ACE-536, are recombinant proteins administered via SC injections every three weeks. They have slightly different binding affinities for ligands affecting RBC production in the bone marrow.

In early testing among healthy volunteers, sotatercept therapy was associated with increased RBC parameters, including improved hemoglobin levels.

The study goal was to determine a safe, tolerable, and effective sotatercept dose in adult patients with β-thalassemia major who are either transfusion dependent (TD) or nontransfusion dependent (NTD). Included patients had β-thalassemia major or intermedia. TD patients had received two or more RBC units per month for six months or more prior to enrollment. NTD patients had received four or fewer RBC units during the six-month period prior to enrollment.

A total of 37 patients stratified in six groups received doses between 0.1 mg/kg and 1.5 mg/kg (SC every three weeks). Efficacy was assessed for NTD patients as a hemoglobin increase from baseline of 1 g/dL or more. For TD patients, it was assessed as the percentage of patients with a 20% or more reduction in transfusion burden. Maximum exposure was 18 months.

At one year, 81% of patients remain in treatment. Dr. Porter said that more NTD patients achieved a maximum hemoglobin level increase of at least 1 g/dL and at least 2 g/dL in the sotatercept 0.3-, 0.5-, and 0.75-mg/kg cohorts compared with the 0.1-mg/kg cohort. Hemoglobin increases of at least 1 g/dL were reported in 67% of patients receiving 0.3 mg/kg and in 100% of patients receiving 0.75 mg/kg. No patients receiving 0.1 mg/kg achieved such increases. Hemoglobin increases of at least 2 g/dL were found in 33% of patients receiving 0.5 mg/kg and in 50% of patients receiving 0.75 mg/kg sotatercept doses. No such increases were reported for lower doses.

Twenty percent or higher reductions in transfusion burden were reported in no patients receiving 0.1 mg/kg, in 33% of patients receiving 0.3 mg/kg, in 50% of patients receiving 0.5 mg/kg, and in 67% of patients receiving 0.75 mg/kg of sotatercept. A third of patients receiving sotatercept 0.75 mg/kg achieved 50% or more reductions in transfusion burden. No patients at lower doses achieved that level of transfusion reduction.

Sotatercept was safe and well tolerated, and the maximum tolerated dose was not reached.

The primary endpoint in Dr. Piga’s study of ACE-536 in β-thalassemia intermedia patients was the proportion of patients with an erythroid response (defined as a hemoglobin increase from baseline of at least 1.5 g/dL) in NTD patients or with a transfusion burden decrease of at least 20% in TD patients. Seven cohorts of patients (N = 24) received doses of 0.2 mg/kg to 1.5 mg/kg for three months.
Continuous lenalidomide outcomes were taken from the FIRST based on treatment-specific utility weights for each health state. PFS and OS associated with each treatment using observed over a lifetime horizon. The model projected average lifetime model to perform this analysis from a U.S. payer perspective multiple myeloma patients. He developed a partitioned survival lenalidomide versus fixed-duration VMP in newly diagnosed analysis comparing the costs and benefits of continuous efficacy to melphalan-prednisone (San Miguel et al., 2013).2 The FDA for this population, has also demonstrated superior OS benefit at an interim analysis compared with a fixed duration VMP. Incremental cost-effectiveness ratios (ICERs) for continuous lenalidomide relative to VMP were $86,126 per QALY gained and $61,509 per LY gained.

“These cost-effectiveness ratios,” Dr. Cavenagh said, “are well within levels published for other recent advances in a front-line oncology setting.” Despite the additional costs incurred with continuous treatment, lenalidomide was cost-effective relative to fixed-duration treatment with VMP because of the extension of clinical benefit, he added.

Ruxolitinib Proves Superior to Best Available Therapy in a Prospective, Randomized, Phase 3 Study (RESPONSE) in Patients With Polycythemia Vera Resistant to or Intolerant of Hydroxyurea

• Alessandro M. Vannucchi, MD, Associate Professor of Hematology, University of Florence, Florence, Italy

Cost-Effectiveness in Newly Diagnosed Multiple Myeloma: Lenalidomide Plus Low-Dose Dexamethasone Versus Bortezomib Plus Melphalan and Prednisone
• Jamie D. Cavenagh, MD, Professor of Hematology, St. Bartholomew’s Hospital, London, United Kingdom

New evidence in multiple myeloma has indicated that health gains are maintained through continuous treatment. In the FIRST trial (Frontline Investigation of Lenalidomide + Dexamethasone Versus Standard Thalidomide), continuous lenalidomide significantly improved PFS and provided an OS benefit at an interim analysis compared with a fixed duration of either 18 months of lenalidomide or the combination of melphalan-prednisone-thalidomide (MPT) in transplantineligible patients (Facon et al., 2013).1 A fixed treatment duration of bortezomib-melphalan-prednisone (VMP), approved by the FDA for this population, has also demonstrated superior efficacy to melphalan-prednisone (San Miguel et al., 2013).2

Given these treatment options, Dr. Cavenagh said, the question naturally arises: What is the balance between costs and benefits for continuous versus fixed-duration therapy?

Dr. Cavenagh’s aim was to conduct a cost-effectiveness analysis comparing the costs and benefits of continuous lenalidomide versus fixed-duration VMP in newly diagnosed multiple myeloma patients. He developed a partitioned survival model to perform this analysis from a U.S. payer perspective over a lifetime horizon. The model projected average lifetime PFS and OS associated with each treatment using observed trial data and estimated quality-adjusted life years (QALYs) based on treatment-specific utility weights for each health state. Continuous lenalidomide outcomes were taken from the FIRST trial, while VMP outcomes came from the VISTA (Velcade as Initial Standard Therapy in Multiple Myeloma) study.

Consistent with prior phase 2 findings, ruxolitinib was superior to best available therapy (BAT) in the phase 3 RESPONSE trial among polycythemia vera (PV) patients who were resistant to or intolerant of hydroxyurea (HU).

PV is a myeloproliferative neoplasm characterized by erythrocytosis, burdensome symptoms (e.g., pruritis), and an increased risk of cardiovascular complications resulting from thrombosis or hemorrhage, Dr. Vannucchi said in a late-breaking clinical trial presentation. A key goal of therapy is to maintain hematocrit (HCT) control (less than 45%). HU is often used as a first-line cytoreductive treatment; however, not all patients achieve HCT control or tolerate therapy with HU.

“With time, about 20% to 25% of patients taking hydroxyurea may become resistant or refractory to the drug,” Dr. Vannucchi said. “This category of patients has an unmet medical need. Also, patients who are resistant to hydroxyurea may represent an advanced stage of PV with significantly reduced survival.”

RESPONSE included 222 HU-resistant or intolerant patients with splenomegaly (at least 450 cm3 by MRI) who required phlebotomy for inadequate HCT control. They were randomized 1:1 to ruxolitinib 10 mg twice a day (up to a maximum of 25 mg twice a day) or BAT (investigator-selected). The primary endpoint was the proportion of patients who achieved both HCT control without phlebotomy from week 8 to 32 (with no more than one phlebotomy between randomization and week 8) and a reduction of at least 35% in spleen volume from baseline by MRI at week 32.

The patients’ median age was 61 years. In BAT-randomized patients, the most common treatments were HU in 59% and interferon/pegylated interferon in 12%, with observation in 15%. The primary combined endpoint at week 32 was achieved in 21% of ruxolitinib patients and in 1% of BAT patients (odds ratio, 28.64; 95% CI, 4.50–12.06; P < .0001). Overall, 77% of continued on page 577
ruxolitinib patients met at least one component of the primary endpoint: 60% of ruxolitinib and 20% of BAT patients achieved HCT control without phlebotomy from week 8 to week 32; 38% of ruxolitinib patients and 1% of BAT patients achieved a reduction in spleen volume of at least 35% at week 32. A durable response (week 48) was achieved in 91% of ruxolitinib patients, with only one patient losing a primary response. At a median follow-up of 81 weeks, 85% of patients (93 of 110) randomized to ruxolitinib were still receiving treatment.

Complete hematological remission at week 32 was achieved in 23.6% and 8.9% of ruxolitinib and BAT patients, respectively ($P = 0.0028$).

Ruxolitinib was generally well tolerated. One thromboembolic event was reported in the ruxolitinib arm, compared with six in the BAT arm. More patients (35.5% versus 29.5%) in the ruxolitinib arm had prior thromboembolic events.

Muscle spasm was more common in the ruxolitinib group than in the BAT group (all grades, 11.8% versus 4.5%; grade 3 or 4 events, 0.9% versus 0). When adjusted for exposure (per 100 patient-years), the rates of adverse events and grade 3–4 adverse events over the course of treatment were lower in patients randomized to ruxolitinib compared with those randomized to BAT (64.7 versus 145.6 and 28.8 versus 44.0).

Dr. Vannucchi concluded that in this population of PV patients, ruxolitinib was superior to BAT in controlling HCT, reducing spleen volume, reducing symptoms, and inducing complete hematological response. “In these patients who are in need of alternative, effective treatments, ruxolitinib may be a potential new treatment option,” he said.

REFERENCES