Anemia Drugs Tied to Deaths in Cancer Patients

BY JANE SALODOF MACNEIL
Senior Editor

SAN FRANCISCO — Cancer patients on erythropoiesis-stimulating agents are 17% more likely to die of any cause while in clinical trials and 6% less likely to be alive at the longest available follow-up, researchers reported at the annual meeting of the American Society of Hematology.

Dr. Julia Bohlius and her collaborators conducted the most far-reaching meta-analysis to date of clinical studies of anemia drugs. Not relying on published literature, the group collected individual patient data from 53 randomized, controlled trials that included 13,933 patients.

This sample included 10,441 patients in chemotherapy trials. The impact of erythropoiesis-stimulating agents (ESAs) was less dramatic in chemotherapy patients, but they, too, had 10% higher mortality while in "the active study phase," and their survival rate was 4% worse at the longest available follow-up.

"ESAs increased on-study mortality and worsened overall survival in cancer patients. For patients undergoing chemotherapy the increase was less pronounced, but could not be excluded," Dr. Bohlius of the University of Bern (Switzerland) said at a press briefing, where she revealed the new data prior to a late-breaking abstract session. Mortality and overall survival were significantly worse ($P = .002$ and $P = .05$, respectively) for all cancer patients in the meta-analysis.

As an acknowledged "uncertainty," chemotherapy patients were not statistically different from 737 patients on radiochemotherapy, 799 on radiotherapy, 266 who were receiving other treatments, and 1,690 who were not treated.

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DR. BOHLIUS

"If you ask two statisticians how to interpret these results, you will get three opinions," Dr. Bohlius said.

Possible next steps include evaluations of post-treatment hemoglobin levels on mortality and the effects of ESAs on thromboembolic events, tumor progression, quality of life, and transfusion needs.

"What we don't really know is why patients die," said her coauthor, Dr. Andreas Engert. He cited two theories—the ESAs promote tumor progression or high hemoglobin levels increase the chance of fatal thromboembolic events.

"I think it is underreporting of thromboembolic events. There [are] no strong data that tumor progression is the cause," said Dr. Engert, chairman and professor of internal medicine, hematology, and oncology at the University of Cologne (Germany). Because these trials enroll cancer patients, many with advanced disease, autopsies that might uncover other causes of death are rarely, if ever, performed.

The results confirm earlier data that led ASH and the American Society for Clinical Oncology to revise their guidelines for ESA use, said Dr. Samuel M. Silver, head of ASH's reimbursement committee. In 2009, "a new guideline panel will be put together by ASH and ASCO, and a discussion of [these] data is going to be incredibly important," said Dr. Silver, assistant dean for research and professor of internal medicine, University of Michigan, Ann Arbor.

Use of ESAs has decreased and blood transfusions are up substantially in the wake of tightened Food and Drug Administration and Medicare directives on ESAs. The drugs are now indicated in cancer for patients with chemotherapy-induced anemia only. The impact ranges from surgeries being postponed because of reduced blood supplies, to reduced availability of outpatient beds for transfusions, to exacerbated comorbidities.

A steering committee guided the meta-analysis, which was done independently in two academic departments. Representatives of the three ESA manufacturers—Amgen Inc., Johnson & Johnson, and Hoffmann-La Roche Inc.—served on the advisory board and contributed data, Dr. Bohlius said, but "had no involvement in the study design, analysis, and interpretation of data and in the writing of the report."

'There [are] no strong data that tumor progression is the cause' of the increase in deaths.

DR. ENGERT

All funding came from two industry-independent sources: the German Ministry of Education and Research and OncoSuisse. Median follow-up was 4 months for the on-study mortality data, and 6 months for overall survival rates.

Dr. Bohlius, Dr. Engert, and Dr. Silver said they had no conflicts of interest. ■

For a related video, go to www.youtube.com/InternalMedicineNews (search for 63487).

Eltrombopag Increases Platelet Counts in Chronic ITP

BY JANE SALODOF MACNEIL
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SAN FRANCISCO — Patients with severe idiopathic thrombocytopenic purpura were eight times more likely to achieve target platelet counts when treated for 6 months with oral eltrombopag in a randomized, placebo-controlled, phase III trial presented at the annual meeting of the American Society of Hematology.

Eltrombopag (Promacta) reduced the odds of bleeding by 76% and of clinically significant bleeding by 65%, vs. placebo. It also lessened the need for rescue medications and concomitant medications in patients with chronic idiopathic thrombocytopenic purpura (ITP) not responsive to previous therapy.

No safety concerns emerged in RAISE (Randomized Placebo-Controlled ITP Study With Eltrombopag), a 197-patient trial sponsored by GlaxoSmithKline and designed to evaluate long-term use of the agent. Adverse events were minor and similar with eltrombopag and placebo.

For patients who are "refractory to the conventional therapy or suffering from the side effects, there is now new hope and a new treatment," principal investigator Dr. Gregory Cheng of the Chinese University of Hong Kong said at a press briefing.

The availability of eltrombopag and romiplostim (AMG-531, Nplate), another new thrombopoietin receptor agonist, represents "a huge change" in thinking about ITP and will greatly benefit patients, according to Dr. Sherrill J. Slichter, an investigator at the briefing, who was not involved in the eltrombopag study and who emphasized that she has no stock in the companies behind these new drugs.

"It has been an enormous boon to the management of these patients to be able to show that some of the ones who fail immunosuppressive therapy in fact respond to an agent that increases platelet production," said Dr. Slichter of Puget Sound Blood Center for the National Heart, Lung, and Blood Institute Transfusion Medicine/Hemostasis Clinical Trials Network in Seattle. Stopping eltrombopag leads to a reduction in platelet counts, she said: "So it is not a cure, but it is a treatment."

Still, despite enthusiasm for Dr. Cheng's results, neither Dr. Slichter nor Dr. Kenneth Kaushansky, president of ASH, was ready to use eltrombopag in patients who still have other options. Indeed, Dr. Kaushansky, chair of the department of medicine at the University of California, San Diego, predicted that hematologists would be slow to adopt eltrombopag and romiplostim.

'There is now new hope and a new treatment' for ITP patients refractory to conventional treatment.

DR. CHENG

"We have not seen significant side effects so far from thrombopoietin-stimulating agents," he said. "But we don't have years and tens of thousands of experiences yet. Once we begin to see [that] the side effect profile of those agents is not significant, then I think confidence will grow in those agents, and I think we will see those agents used earlier."

Dr. Cheng agreed that, in his own practice, he still reserves eltrombopag for chronic patients who have failed to respond to other proven therapies. "My first line of therapy will still be corticosteroids," he said, concurring that potentially curative treatments, including splenectomy, should be tried before potentially lifelong treatment with eltrombopag.

An exception might be an ITP patient scheduled for surgery, Dr. Cheng suggested. Currently, the patient might be admitted to a hospital for preparation with intravenous immunoglobulin, but 2 weeks of oral eltrombopag therapy could be an outpatient alternative. "Then they have the surgery and can stop the medication afterward," he said.

RAISE randomized adults with platelet counts below 30,000 mcL who had failed at least one other ITP therapy. While 135 patients received a starting dose of 50 mg of eltrombopag once daily, another 62 patients received a placebo. Depending on response, the trial allowed titration of the eltrombopag dose up or down in a range of 25-75 mg once a day.

Investigators set the primary end point as achieving platelet counts between 50,000 and 400,000 mcL. Dr. Cheng said that 75% of the eltrombopag cohort reached target, vs. 28% of those on placebo. This was true regardless of splenectomy status. The odds ratio for achieving a response with eltrombopag was 8.2.

Median counts were 16,000 mcL in both cohorts before the initiation of treatment, and never went above 30,000 mcL in the placebo group, according to data released by GlaxoSmithKline. In the eltrombopag cohort, it rose to 36,000 mcL after 1 week, and thereafter ranged from 52,000 mcL to 91,000 mcL during the study. The median returned to baseline within 2 weeks of stopping eltrombopag at the end of the study.

Secondary end points favoring eltrombopag included more patients stopping or reducing simultaneous ITP medications (59% vs. 32%) and fewer patients needing rescue therapy (19% vs. 40%).

Dr. Cheng disclosed being a consultant to and receiving honoraria from GlaxoSmithKline. His coinvestigators included employees of the company and holders of equity ownership. ■

For a related video with Dr. Cheng, go to www.youtube.com/InternalMedicineNews (search for 63486).