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IV Iron Added to ESAs Improves Results in Chemotherapy-Induced Anemia

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September 15, 2008 (Stockholm, Sweden) — In patients with chemotherapy-induced anemia, the addition of intravenous (IV) iron to an erythropoiesis-stimulating agent (ESA) improves the hematologic response so that patients reach hemoglobin targets more quickly. This can cut down on the amount of ESA used, with cost savings of around $100 per patient per week, said Michael Auerbach, MD, a hematologist in private practice in Baltimore, Maryland.

"Oncologists should embrace IV iron and use it together with ESAs to maximize the use of these products," he said, adding that ESAs "have had a massively positive impact on our patients over the last decade."

Dr. Auerbach presented the results here at the 33rd European Society for Medical Oncology Congress from a phase 3 trial of 238 patients with chemotherapy-induced anemia treated with darbepoetin (*Aranesp*, Amgen) with and without iron. The results showed that a greater proportion of patients who received IV iron in addition to the ESA reached the target hemoglobin level of 13 g/dL (37% vs 21% of those not receiving iron), and also that hemoglobin levels rose 1.5 g/dL or more within 21 days (83% vs 57%) in a greater proportion of patients.

These results demonstrate that adding IV iron to ESAs improves results. This is the sixth trial that has shown such a benefit, Dr. Auerbach commented. Like this trial, 4 of the 5 previous trials were conducted in patients with chemotherapy-induced anemia, but 1 was carried out in patients with lymphoproliferative malignancies and cancer-induced anemia, he told *Medscape Oncology*.

These results are "certainly quite impressive, and they certainly show once again that you can improve on the results with ESAs when you add intravenous iron," commented Matti Aapro, MD, from the Institut Multidisciplinaire d'Oncologie, in Genolier, Switzerland, who was a discussant for this presentation. However, he also outlined several concerns and unanswered questions about this use of IV iron in the cancer setting.

Oncologists Should Embrace Use of Iron

"The take-home message is clear," Dr. Auerbach commented in an interview: "adding IV iron to ESAs improves the results, and can also lead to substantial cost savings." Dr. Auerbach said that he would encourage all oncologists to use IV iron in addition to ESAs in virtually all of their patients with chemotherapy-induced anemia. This is what he practices; he withholds IV iron only in patients who have a transferrin saturation test of more than 50%.

Oncologists are not currently using IV iron this way, he said. Estimates based on sales figures from the United States suggest that only 15% to 20% of oncologists are adding IV iron to ESAs in patients with chemotherapy-induced anemia, and he suspects that the figures in Europe are even lower. This is in contrast to what is happening in the renal field, where nearly all nephrologists add IV iron to ESAs in patients on dialysis, and have been doing so since 1994, when studies first came out supporting such use.

However, Dr. Aapro said that many questions remain about the use of IV iron in this setting. One is safety, and he said that, despite Dr. Auerbach's positive comments, so far there has been no safety

signal in more than 1000 patients in clinical trials. He feels that "we do not have enough patients to be certain about safety."

Dr. Aapro dismissed allergic reactions to iron as a minor issue, saying that they are not a problem with modern iron preparations. "Oncologists are used to managing allergic reactions to cytotoxic agents, so even if the problem did exist, it would be annoying but not a major issue," he commented in an interview with *Medscape Oncology*.

However, there is a concern that adding iron to cytotoxic agents that have deleterious effects on the heart could increase cardiotoxicity. There are also concerns that iron can theoretically increase patients' susceptibility to infections, which has been suggested by studies in the renal field, and that iron can theoretically promote tumor growth, according to preclinical work that has shown that iron chelation can reduce tumor growth, Dr. Aapro said.

Dr. Auerbach countered these comments at a subsequent press conference, and said that the data from the clinical trials so far do not suggest that there is any effect on tumor progression. In fact, the trend was toward a slight improvement in cancer-related parameters, although was not statistically significant.

Dr. Aapro also raised the concerns about iron in a wider context, pointing out that the alternative for many of these patients is blood transfusions, and "transfusions certainly are not safe," he said. Regulatory authorities have recently recommended the use of blood transfusions in place of ESAs in cancer patients with chemotherapy-induced anemia, but there are no regulatory data to show that transfusions are a safe option, he said. Transfusion reactions are not uncommon, and there is a potential for iron overload, he pointed out. In addition, there is a concern that transfusions can sensitize patients before they receive allotransplants for lymphoma and leukemia, and there are some data to show that transfusions can decrease survival in colon cancer patients after surgery, he added. There is also the issue of supply — blood banks do not have unlimited supplies, and overall safety, as far as transmitting infection through a transfusion, is not guaranteed in all countries in the world, he said.

Dr. Aapro said that clinicians are using IV iron to improve results in cancer patients, in those who have been shown to be iron deficient, and in those who are taking EASs but who are not iron deficient (as in the current study). But there are practical questions that still need to be answered, he said. Currently, there is no preferred product or optimal dosing schedule. Many different iron preparations are available, and they are used in different schedules, according to how the studies were performed. Also, the question of whether iron should be used before ESAs has never been addressed, he pointed out.

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