Published in final edited form as:
Am J Hematol Oncol. 2008 August 1; 7(8): 327–332.

Risks of Venous Thromboembolism and Mortality Associated With Erythropoiesis-Stimulating Agents for the Treatment of Cancer-Associated Anemia

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Findings from our recently published meta-analysis demonstrate increased risks of venous thromboembolism and mortality with the administration of erythropoiesis-stimulating agents (ESAs) to treat anemic cancer patients.1 ESAs, which are supportive care drugs that include recombinant erythropoietin and darbepoetin, were approved in 1993 and 2002, respectively, for the treatment of chemotherapy-induced anemia.2,3 Following their approval, concerns regarding increased risk of tumor progression and venous thromboembolism (VTE) have been raised.4 In 2003, two trials identified poorer survival among ESA-treated breast cancer patients receiving chemotherapy and head and neck cancer patients receiving radiotherapy.5,6 Additionally, two systematic overviews published in 2006 found increased VTE risks associated with ESAs but did not identify mortality risks.7,8 We therefore conducted a meta-analysis to comprehensively evaluate venous thromboembolism and mortality risks associated with ESA use.

Methods

The Cochrane 2006 systematic overview served as the primary data source for this analysis, and studies reported more recently were added. The 2006 Cochrane overview evaluated 42 trials with 8,167 patients for overall survival and 38 trials with 6,769 patients for VTE.9 Our meta-analysis excluded one trial that was included in the Cochrane overview because it evaluated patients with myelodysplastic syndrome rather than cancer and added 13 new trials (n=5,369 patients).10-22 Mortality and VTE rates were extracted from a total of 51 clinical trials with 13,611 patients and 38 trials with 8,172 patients, respectively. Data sources included published trials and systematic reviews as well presentations from the 2007 FDA Oncologic Drugs Advisory Committee meeting. Trials included were both independent and industry sponsored. Effect estimates for hazard rates (HR), relative risks (RR), and 95% confidence intervals (CIs) were derived.1

Results

Results from the mortality analysis identified a 10% increased risk of mortality associated with the use of ESAs for anemic cancer patients (HR=1.10; 95% CI, 1.01-1.20). Moreover, a 57% increased risk of VTE was noted with the use of ESAs for this indication (RR: 1.57;

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95% CI, 1.31-1.87). These associations were not dominated by a small number of studies; the largest 8 trials each contributed 5% to 9% of the total patients included.1

Trials included in this analysis varied with respect to study drug, sample size, treatment duration, concomitant treatments, and cancer types. Epoetin alfa or epoetin beta, two variations of erythropoietin, were evaluated in 40 trials and darbepoetin was evaluated in 11 trials. A median of 223 patients were included, ranging from 30 to 939 patients. Additionally, the duration of ESA treatment ranged from 6 to 52 weeks. The trials included patients who experienced cancer-related anemia as well as treatment-related anemia. While 28 trials included patients who were concomitantly receiving chemotherapy, other trials included concomitant treatments of radiotherapy (3 trials), chemoradiotherapy (7 trials), and palliative radiotherapy (1 trial). Three trials did not report concomitant treatments, and patients from 7 trials evaluating cancer-related anemia did not receive concomitant treatment. Twenty-six trials evaluated single disease populations including lung cancer, breast cancer, head and neck cancer, cervical cancer, ovarian cancer, lymphoma, and multiple myeloma.1

Discussion

This analysis confirmed previous findings of an increased risk of VTE associated with ESAs for the treatment of anemic cancer patients and also identified a statistically significant increased risk of mortality for use of ESAs within this setting. Given that ESAs are widely used within the oncology setting as a supportive care drug, these findings have important clinical and policy implications. Risks regarding ESA administration to cancer patients have been addressed by notifications disseminated by the FDA and ESA manufacturers, basic science reports, and the FDA Oncologic Drugs Advisory Committee.

In January 2008, the FDA released an advisory describing increased risks of tumor promotion and decreased survival based on findings from the PREPARE (preoperative epirubicin, paclitaxel, darbepoetin alfa) study including patients with advanced breast cancer and the GOG-191 (National Cancer Institute Gynecologic Oncology Group) study including patients with cervical cancer.23 Three safety notifications have been distributed by ESA manufacturers. In March 2007, ESA manufacturers added a black box warning for the first time to the FDA-approved package insert, describing increased VTE and cardiovascular and mortality risks.24 Manufacturers revised the black box warning for ESAs in November 2007 and again in March 2008. In November 2007, the warning indicated that randomized trials identified more rapid cancer progression and shortened overall survival among patients with advanced breast, head and neck, lymphoid, and non□small cell lung cancer. The warning also indicated that ESAs should only be used to treat anemia that occurs in patients with cancer while they are undergoing chemotherapy.25 In March 2008, the revision described faster tumor growth and increased mortality risks with ESAs versus controls based on the aforementioned FDA advisory.26

Debate exits regarding the identification of erythropoietin and erythropoietin receptor expression in a wide range of solid human tumor types.27,28 The specific effect(s) of ESAs in patients may depend upon tumor type. Additionally, erythropoietin may act as a proangiogenic factor, potentially aiding the tumor's ability to recruit a blood supply.29 Many provocative issues remain to be clarified regarding the specific action(s) of ESAs on human cancer cells.

The FDA Oncologic Drugs Advisory Committee met in March 2008 to discuss findings regarding the use of ESAs in the cancer setting and to vote on policy recommendations for this indication. The committee members voted that ESAs should not be used for patients

receiving potentially curative therapies. Additionally, the committee voted to restrict the use of ESAs from breast or head and neck cancer patients based on findings of increased risks within these populations.30

In conclusion, our meta-analysis confirms the risks associated with ESA use for anemic cancer patients that have been addressed by several regulatory organizations, scientific findings, and an FDA advisory committee. The exact mechanism by which ESAs may affect survival of cancer patients is incompletely understood, yet associated risks are apparent. Our findings, in conjunction with other safety advisories, suggest that ESA use within the cancer setting should follow a doctor and patient discussion of associated risks. ♦

Acknowledgments

Supported by grants from the National Cancer Institute (1R01CA 102713-01 and P 30 CA60553).

Author disclosures: Dr Bennett has previously served as a consultant to Amgen and has received grant support from Amgen.

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