

Risk of Venous Thromboembolism and All-Cause Mortality in Cancer Patients Treated with Epoetins either with or without Transfusions versus Cancer Patients Treated with Transfusions alone

Abstract

Background: Erythropoiesis-stimulating agents (epoetins) are recombinant human erythropoietins indistinguishable from the naturally occurring human erythropoietin, a hormone that is produced by the kidneys and that stimulates the production of red blood cells from the bone marrow. Epoetin-containing medicines are used to treat anemia in patients with cancer who are receiving chemotherapy and in patients with chronic kidney disease.

In the last years, questions about epoetin safety were raised regarding venous thromboembolism (VTE) and increased mortality. These evolving safety issues prompted various studies investigating the risks and benefits of epoetins in cancer patients and in patients with chronic kidney disease. A recently updated Cochrane review including a total of 91 trials with more than 20,000 cancer patients by Tonia et al. for example found strong evidence that epoetins increase mortality during the active study period (hazard ratio (HR): 1.17; 95% confidence interval (CI): 1.06-1.29) and some evidence that epoetins decrease overall survival (HR: 1.05; 95% CI: 1.00-1.11). The risk ratio (RR) for thromboembolic complications was increased in patients treated with epoetins compared to those not receiving epoetins (RR: 1.52; 95% CI: 1.34-1.74).

These increasing concerns about the safety of epoetins especially when targeting high hemoglobin (Hb) levels have caused several statements, recommendations and warnings by the regulatory agencies on the use of epoetins in cancer patients and in patients with chronic kidney disease. In June 2008 the Committee for Medicinal Products for Human Use (CHMP) concluded that in cancer patients with reasonably long life-expectancy anemia should be corrected with blood transfusions, because the benefit of using epoetins does not outweigh the potential risk of tumor progression and shorter overall survival.

However, elevated risks for VTE and mortality have not only been reported for epoetins but also with regard to blood transfusions.

Objective: The objective of this study was to assess the risk of VTE and all-cause mortality in incident cancer patients receiving epoetin treatment either with or without additional transfusions compared to cancer patients receiving blood transfusions alone in Germany in a real world setting.

Methods: Analyses were based on a cohort of incident cancer patients treated with epoetin and/or transfusions from January 01, 2004 through December 31, 2009. Cohort entry was defined as first treatment with epoetin or transfusions after being continuously insured for at least twelve months. Patients treated with epoetin and/or transfusions in the twelve months preceding cohort entry were excluded. Incident cancer patients were defined as all patients with at least one diagnosis of cancer or a code indicating chemotherapy within six months before cohort entry, but no diagnosis of cancer or code indicating chemotherapy between six and twelve months before cohort entry. Cohort exit was defined as the first of the following dates: End of insurance period (including death of any cause) or end of study period.

Epoetin treatment was assessed via outpatient prescriptions and included all epoetins irrespective of the licensed indications. Transfusions were assessed via in- and outpatient codes. Patients diagnosed with a cancer type with unfavourable prognosis defined as a 5-year relative survival rate below 30% were assigned to a separate group. Additionally, chronic renal failure (CRF) was assessed as other potential indication for treatment with epoetin and/or transfusion.

VTE was defined as deep vein thrombosis of the leg/hip or pulmonary embolism and all-cause mortality was defined as death of any cause.

Co-morbidities including risk factors for VTE were assessed in the twelve months preceding cohort entry. To measure and adjust for patients' disease burden, an adaptation of the Charlson Co-morbidity Index was used. Co-medications associated with an increased risk of VTE were assessed in the 90 days preceding the VTE event. Additionally, dispensations of antithrombotic agents were assessed and considered as a protective factor.

A nested case-control analysis using conditional logistic regression was conducted to estimate adjusted odds ratios (ORs) with corresponding 95% CIs for VTE and treatment with epoetin and/or transfusions in two different time windows.

Further, multivariable Cox proportional hazard regression models were applied to assess the risk of all-cause mortality comparing patients receiving epoetin treatment to those treated with transfusions. Therefore a respective time-dependent exposure variable was included.

Results: During the study period 69,888 incident cancer patients receiving a first time treatment with epoetin or transfusion could be identified. The median age at cohort entry was 69 years and more than half (52.7%) of the patients were female. During time in cohort 3,316 patients (4.7%) were diagnosed with VTE and overall 32,345 patients (46.3%) died in the study period.

The conditional logistic regression analysis yielded an adjusted OR of 1.31 (95% CI: 1.03-1.65) for epoetin treatment in the 28 days preceding the index date compared to no

treatment. For transfusions an OR of 2.33 (95% CI: 2.03-2.66) was found and the VTE risk in patients being treated with epoetin and transfusions was 2.24 (95% CI: 1.34-3.77). Examining the time window of 90 days preceding the index date revealed a slightly higher OR for epoetin use and a slightly lower OR for transfusions.

The Cox model showed an adjusted HR of 0.93 (95% CI: 0.89-0.97) for mortality comparing epoetin treatment with transfusions. Excluding patients also diagnosed with CRF yielded an HR of 0.99 (95% CI: 0.94-1.04). When restricting the analyses to patients diagnosed with cancer with unfavourable prognosis, an HR of 1.04 (95% CI: 0.98-1.11) was found.

Discussion: In the two different time windows examined, our study found an increased VTE risk associated with use of epoetin of a comparable magnitude as reported in the literature. We did not find an increased mortality associated with epoetins as indicated by recent meta-analyses. In contrast, our study showed a slightly lower mortality among patients receiving epoetins compared to those treated with transfusions. This might be explained by the fact that the prevalence of transfusions in our study was considerably higher than in other studies included in the meta-analyses and transfusions have been shown to be associated with a higher mortality themselves. However, confounding by indication/disease severity can also not be ruled out, since we did not have information on the assumed life-expectancy or the anemia's severity of the patients, which might be associated with the treatment choice.