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Erythropoiesis-stimulating agents in gynecological malignancies: A study-level meta-analysis

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ABSTRACT

This meta-analysis was planned to define the role of erythropoiesis-stimulating agents (ESAs) in gynecological cancer patients, receiving myelosuppressive treatment.

Pubmed, Medline and Scopus were searched to select English-language articles. Only randomized controlled trials (RCTs) were included. Endpoints were incidence of transfusions, thrombotic events (TE), deaths, and failures. Odd ratio (OR) with 95% confidence interval (CI) was calculated using fixed or random effects model.

In seven RCTs ESAs studies of 892 patients under treatment, use of ESAs correlates with a significant reduction of transfusions rate (OR = 0.35; 95% CI: 0.19–0.65; $p = 0.008$). OR for overall mortality was 1.10 (95% CI 0.82–1.49; $p = 0.53$). ESAs OR for disease failure in 5 studies was 1.71 (95% CI: 0.90–3.24; $p = 0.1$).

This meta-analysis, even if limited by few RCTs, suggests that ESAs reduce transfusions without increasing mortality or disease progression in gynecological cancer patients receiving treatment.

1. Introduction

Gynecological cancers are the one at highest risk of anemia (Ludwig et al., 2004). In these patients, anemia represents one of the main problem and it has been associated with an increase in postoperative morbidity and mortality, an increase in trans-

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fusion rates, and a decrease of either quality of life and survival rates (Dunne et al., 2002; Caro et al., 2001). The traditional treatment of anemia is blood transfusions although in the last decades erythropoiesis-stimulating agents (ESAs) have acquired increasing consensus (Bellati et al., 2007).

Nonetheless, in the recent years, clinical studies and meta-analyses, have raised concerns on the

use of ESAs, suggesting that they can increase the rates of progression of disease and of thrombotic events (TE), decreasing overall survival (Oster et al., 2012). Therefore, their use in clinical practice has become controversial.

This meta-analysis was performed to bring the most rigorous and scientific evidence regarding the potential effects of ESAs in gynecological cancer.

2. Materials and methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed to perform the meta-analysis. We conducted a systematic literature review of ESAs studies in gynecological cancers published from January 1996 to December 2014. Literature electronic databases (Pubmed, Medline and Scopus) were searched for "ovarian" or "cervical", "cancer", "erythropoietin", and "randomized" in title and abstract. Only clinical trials, written in English, were considered. Included studies were randomized phase III trials of gynecological cancer patients treated with ESAs compared with control patients who received placebo or best standard treatment of anemia. Reference lists of previously published reviews were explored. Review articles, commentaries and letters were not included. Conference abstracts were not considered because of the insufficient data provided by the authors.

Two independent reviewers (CM and FDF) selected the identified studies based on the title and abstract. If the study's topic could not be ascertained from its title or abstract, the full-text version would be retrieved for evaluation. Disagreement was resolved by discussion or consensus or with a third party (LM).

In the closer evaluation of potentially eligible articles, when two articles appeared to report results with overlapping data, only the data representing the most recent publication date or with the larger sample size were included in the meta-analysis. We made every attempt to eliminate redundancy in the data represented in our meta-analysis. From all including studies were obtained: first author' surname, publication year, sample size of cases and controls, treatment and detection rate.

2.1. End-points

Endpoints were the incidence of transfusions, TE, deaths, and failures. Data were estimated during the median follow-up of each trial. Failures were distinguished in persistence or progression disease during treatment, and recurrence, defined as the re-emerge of disease after treatment and after a 6 months period of complete regression (Lok et al., 2015).

2.1.1. Subgroup analysis

Based on baseline hemoglobin level $\leq$12 g/dL–was performed to evaluate whether this factor could influenced incidence of TE.

2.2. Statistical analysis

The analysis used odds ratio (OR) to compare results for the ESAs treated patients to control patients. The pooled OR was calculated using a fixed-or a random-effect models. If there were no events in both groups, the trial was omitted from the meta-analysis because it did not provide information about relative probability.

Forest plot were used for graphical representation of each study and pooled analysis. The size of every box represents the weight that the corresponding study exerts in the meta-analysis; confidence intervals (CI) of each study are displayed as horizontal line through the box. The pooled OR was symbolized by a solid diamond at the bottom of the forest plot and the width of the square represents the 95% CI of OR. OR, variance, 95% CI and SE for each study were extracted or calculated based on the published studies according to the methods described by Tierney et al. (2007). A significant two-way p-value for comparison was defined as $p < 0.05$. Statistical heterogeneity between studies was examined using both the Cochrane Q statistic (significant at $p < 0.1$) and the I^2 value (significant heterogeneity if >50%) (Higgins et al., 2003). Statistical analysis was performed by Review Manager 5.0 (http://www.cochrane.org). Publication bias was examined using analyses described by Egger and Begg Egger et al. (1997) and Begg and Mazumdar (1994).

3. Results

The literature search identified a total of 30 potentially relevant article types. Articles were excluded because of subject not related to the study ($n = 8$) nor published in English ($n = 3$), review ($n = 4$) and editorial ($n = 1$). Three studies were not considered because they were a phase I/II trial ($n = 1$), a non randomized comparison ($n = 1$) and a retrospective analysis ($n = 1$), respectively. One study was excluded due to its design based on a controlled and an uncontrolled treatment phased. Out of 10 applicable clinical studies, 3 were eliminated due to different end-point analysis. At the end of the review process, 7 studies were included in the meta-analysis and they evaluated 892 gynecological cancer patients (Table 1) (Wilkinson et al., 2006; ten Bokkel Huinink et al., 1998; Kurz et al., 1997; Blohmer et al., 2011; Gupta et al., 2009; Thomas et al., 2008; Strauss et al., 2008).

Chemotherapy was given to patients in 3 (42.9%) of 7 studies included in the meta-analysis, radiochemotherapy in 3 (42.9%), and chemotherapy followed by radiotherapy in 1 (14.2%). Patients were treated with the ESAs epoetin alfa (in 2 studies), epoetin beta (in 2 studies), or not specified recombinant human erythropoietin (in 3 studies). Survival was the primary end-point in 3 (42.9%) studies, and the secondary end-point in 2 (28.6%). Transfusion and thromboembolic events were evaluated in 7 and 6 studies (85.7%), respectively.

3.1. Transfusion

All seven studies were analyzed. The OR analysis for reduction in transfusions rate showed a consistent results for ESAs group, with an overall OR of 0.35 (95% CI: 0.19–0.65; $p = 0.008$). The I^2 showed moderate heterogeneity among the studies (68%). See Fig. 1.

3.2. Thrombotic events

A total of six studies reported data on thrombotic events, but actually Gupta et al. trial (Gupta et al., 2009) was not considered in the analysis because there were no events in both groups.

The OR for thrombotic events was 2.83 (95% CI: 1.29–6.22; $p = 0.009$) for ESAs compared to control group. The I^2 showed absence of heterogeneity among the studies (0%).

Subgroup analysis for thrombotic events was conducted using baseline Hb $\leq$ 12 as cut-off. The OR resulted 4.87 (95% CI: 0.84–28.06; $p = 0.08$; $I^2 = 0\%$) for ESAs group.

Details are presented in Fig. 2.