Original Study

Effect of Bleomycin Administration on the Development of Pulmonary Toxicity in Patients With Metastatic Germ Cell Tumors Receiving First-Line Chemotherapy: A Meta-Analysis of Randomized Studies

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Abstract

In a trial-level meta-analysis of randomized studies, bleomycin administration was independently significantly associated with the development of pulmonary toxicity in patients with metastatic germ cell tumors receiving first-line chemotherapy. This effect was mainly seen with respect to all-Grade pulmonary toxicity. This study provided a further argument in favor of reducing the burden of curative chemotherapy in these highly curable malignancies.

Background: Limited information is available about the effect of bleomycin administration on the development of pulmonary toxicity in metastatic germ cell tumors (GCT). **Patients and Methods:** A literature search was conducted to identify randomized trials of first-line chemotherapy for GCT. We conducted univariate and multivariate analyses using random effects models to evaluate the predictive role of bleomycin administration in the development of all Grade and Grade 3 to 4 (G3-4) pulmonary toxicity. The results were adjusted for length of follow-up, prognostic risk group, year of treatment, presence of lung metastases, and primary mediastinal GCT. **Results:** Fifty-three study arms of 25 phase II and III trials encompassing 6498 patients were selected: 40 that used bleomycin (n = 5093) and 13 that did not (n = 1405). The pooled probability of all-Grade pulmonary toxicity in the bleomycin and nonbleomycin arms was 11.7% (95% confidence interval [CI], 8.4%-16.0%) and 1.7% (95% CI, 0.7%-4.2%), respectively. Univariate analysis indicated that bleomycin administration was associated with the incidence of all-Grade (odds ratio [OR], 7.57; 95% CI, 2.84-20.18; Wald test $P < .001$) and G3-4 pulmonary toxicity (OR, 5.19; 95% CI, 1.57-17.16; $P = .007$). Multivariate analysis showed a significant association of bleomycin administration with the incidence of all-Grade pulmonary toxicity (OR, 4.14; 95% CI, 1.36-12.59; $P = .012$) and a trend toward significance for G3-4 toxicity (OR, 2.24; 95% CI, 0.91-5.51; $P = .080$). **Conclusion:** We quantified the bleomycin-associated effect on the development of pulmonary toxicity in patients with GCT who received first-line chemotherapy. This information might be useful for planning clinical trials aimed at reducing chemotherapy as well as to inform patients in the clinic.

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Introduction

Metastatic germ cell tumor (GCT) is a curable advanced cancer, and the survival possibilities for these patients have gradually improved in recent decades.[1,2] The possibilities for young adult patients to survive for several years after completion of chemotherapy and/or surgery or radiotherapy have led investigators to refine follow-up and supportive care strategies for this disease. The current guidelines for treating metastatic disease recommend 3 or 4 cycles of BEP (bleomycin, etoposide, and cisplatin) chemotherapy, according to the prognostic risk group, and 4 cycles of etoposide and cisplatin as an alternative option for patients with low-risk GCTs.[3-6]

Many specialists consider addressing late toxicity a high priority in the management of GCTs. Bleomycin-induced pulmonary toxicity is a well recognized side effect.[7] Several trials have shown that it develops in up to 40% to 45% of bleomycin-treated cases, in either a clinical or subclinical course, and results in death in 1% to 3% of cases. The pathophysiology of bleomycin toxicity is attributable to drug-induced endothelial damage of the lung vasculature, which adds to the effects of cytokine- and oxygen radical—mediated damage. Genetic susceptibility might be an additional factor. In approximately 5% to 10% of cases, pulmonary fibrosis develops after long-term follow-up.[8-15] To date, efforts to identify clinical predictors for the development of bleomycin-induced toxicity in GCT have relied on small retrospective series or case reports. There is no consensus on lung function tests or other examinations to prevent lung damage or to support the administration of nonbleomycin-containing chemotherapy in certain patients at high risk of developing lung fibrosis. Therefore, early diagnosis of lung damage is important during follow-up after completion of chemotherapy.

Several authors have attempted to identify clinical factors to predict the development of bleomycin-induced toxicity. One of the most relevant studies (ie, a United Kingdom study in a large patient population), identified the following factors: increasing age, poor renal function tests, stage IV disease, and a total dose of bleomycin $>$ 300,000 IU.[11] Therefore, because of the association between bleomycin cumulative dose and the development of pulmonary fibrosis after long-term follow-up, 300,000 IU is currently the recommended maximum cumulative dose. Improving our understanding of pulmonary toxicity associated with the administration of bleomycin-containing chemotherapy might help to guide physicians in selecting alternative treatments in daily practice, reduce the burden of chemotherapy in low-risk GCT patients in clinical trials, and provide more effective patient counseling. For these reasons, we conducted a trial-level meta-analysis on the incidence of pulmonary toxicity in patients with GCTs after administration of bleomycin chemotherapy.

Patients and Methods

Search Strategy and Data Abstraction

From June to October 2015, we performed a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[16] Eligible randomized or nonrandomized phase II and III studies were identified in PubMed, EMBASE, and meeting abstracts presented at congresses of the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology, the American Association of Cancer Research, and Genitourinary Cancers Symposiums (Figure 1).

The following inclusion criteria were used: publication between 1990 and 2015, $>$ 50 patients enrolled, male sex, randomized trials, and phase II or III trials of first-line combination chemotherapy for metastatic GCT. High-dose or dose-dense chemotherapy studies were also included. The principal exclusion criteria were overlapping publications, lack of relevant outcome data, reporting only on patients treated before 1990, and regimens that combined chemotherapy with molecularly targeted therapies. The population, intervention, comparison, and outcome strategy was used, and the following search string was used: 'germ cell tumor'/exp or 'testis cancer'/exp and 'chemotherapy'/exp or 'cancer chemotherapy'/exp or 'systemic therapy'/exp and 'randomised controlled trial'/exp. Other queries with relevant variants and filters were subsequently added and integrated by searching the ASCO Web site. Search results were independently reviewed by 2 authors (A.N., K.O.). The full articles were retrieved for further qualitative review.

Statistical Analysis

The primary objective of the study was to compare the incidence of all-Grade and Grade 3 to 4 (G3-4) pulmonary toxicity between study arms with and without bleomycin chemotherapy. Descriptive statistics were used to summarize information across all trials and were grouped according to the presence or absence of bleomycin in the treatment. The predicted total dose and number of administrations of bleomycin were used instead of the actual numbers (not reported in most articles). Random effects models with inverse variance weighting were used to pool trial-level data separately in each treatment arm. We used random effects models because the Q test and I^2 statistic indicated heterogeneity among the studies (Q statistic P value $<$ 10% and/or $I^2 >$ 25%). Outcome comparisons between the treatment groups were performed using random effects univariate and multivariate models. The following variables were selected as adjustment factors on the basis of clinical expertise: length of follow-up (months, continuous), International Germ Cell Cancer Collaborative Group (IGCCCG) risk category when available (older classifications were not accounted for), year of treatment ($\leq$ 1997 vs. $>$ 1997), percentage of patients with lung metastases, and percentage of patients with primary mediastinal GCT. Missing data were handled as a separate category in each case. Publication bias was evaluated by visually inspecting funnel plots and using the Egger test for bias. The statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC) and R software (http://www.Rproject.org).

Results

Evidence Synthesis

Using the search criteria described previously, we identified 127 studies (31 from EMBASE alone, 96 from EMBASE and MEDLINE), published between 1990 and 2015. Figure 1 outlines the selection process and reasons for study exclusion. Supplemental Table 1 (available in the online version) shows the principal characteristics and outcomes at the single-study level. A total of 53 arms of 25 phase II and III trials encompassing 6498 patients were selected: 40 used bleomycin (n = 5093) and 13 did not

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