Original Study

Impact of Granulocyte-colony Stimulating Factor on Bleomycin-induced Pneumonitis in Chemotherapy-treated Germ Cell Tumors

Edmond M. Kwan,[1] Sophie Beck,[1] Eitan Amir,[2] Michael A. Jewett,[3] Jeremy F. Sturgeon,[2] Lynn Anson-Cartwright,[4] Peter W. Chung,[4] Padraig R. Warde,[4] Malcolm J. Moore,[5] Philippe L. Bedard,[2] Ben Tran[1,2]

Abstract

The impact of granulocyte-colony stimulating factor use on bleomycin-induced pneumonitis in patients with germ cell tumor is not clearly defined. This analysis of over 200 patients with germ cell tumor treated with bleomycin-containing chemotherapy found no association between the use of granulocyte-colony stimulating factor, and the incidence or severity of bleomycin-induced pneumonitis. The decision to use growth factor support in this population should continue to be individualized.

Objective: To examine the impact of granulocyte-colony stimulating factor (G-CSF) use on the incidence and severity of bleomycin-induced pneumonitis (BIP) in patients with germ cell tumor (GCT) receiving first-line chemotherapy. **Patients and Methods:** Clinical data from our institutional GCT database was complemented by review of radiology, pharmacy, and medical records. All patients receiving first line chemotherapy between January 1, 2000 and December 31, 2010 were included. Patients receiving at least 1 dose of G-CSF were identified. BIP was graded using Common Terminology Criteria for Adverse Events criteria. Logistic regression was used to explore predictors for risk and severity of BIP. Statistical significance was defined as $P < .05$. **Results:** Data on 212 patients with GCT treated with a bleomycin-containing chemotherapy regimen were available. The median age was 31 years. The median follow-up period was 36.7 months. BIP occurred in 73 patients (34%), a majority (n = 55) of which were asymptomatic events (Common Terminology Criteria for Adverse Events, grade 1). G-CSF use was not associated with increased risk of BIP in multivariable analyses (odds ratio, 1.60; $P = .13$), nor was it associated with increased severity of symptomatic BIP (on average 1.22 grades higher; $P = .09$). There was a non-statistically significant trend towards greater risk of BIP in patients that developed renal impairment during chemotherapy treatment (odds ratio, 2.56; $P = .053$). **Conclusion:** In patients with GCT receiving first line chemotherapy, G-CSF use is not associated with an increased risk of BIP. Furthermore, the use of G-CSF did not have any significant effect on the severity of BIP events. Clinicians are reminded to be vigilant of patients that develop renal impairment while undergoing chemotherapy treatment, given the greater risk of BIP.

Clinical Genitourinary Cancer, Vol. ■, No. ■, ■-■
Keywords: G-CSF, Growth factors, Lung injury, Pulmonary toxicity, Testicular cancer

Introduction

Considerable progress has been made in the medical management of advanced germ cell tumors (GCTs) as a result of the introduction of cisplatin to chemotherapy regimens in the mid-1970s.[1] Although prognosis varies according to International Germ-Cell Cancer Collaborative Group (IGCCCG) risk classification, cure rates

[1]Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia
[2]Department of Medical Oncology
[3]Department of Surgical Oncology
[4]Department of Radiation Oncology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, Ontario, Canada
[5]British Columbia Cancer Agency, Vancouver, British Columbia, Canada

Submitted: May 15, 2017; Revised: Aug 27, 2017; Accepted: Aug 28, 2017

Address for correspondence: Dr Ben Tran, MBBS, FRACP, Department of Medical Oncology, Peter MacCallum Cancer Centre, 305 Grattan St, Parkville, VIC 3050 Australia
E-mail contact: Ben.Tran@petermac.org

1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2017.08.012

approach 80% for men with advanced stage GCT.[2] Given the high rate of cure, the reduction in treatment-related toxicity is of critical importance.

Multiple studies have established BEP (bleomycin, etoposide, and cisplatin) as the standard first-line chemotherapy regimen for disseminated GCT.[3-5] It is well-recognized that the administration of bleomycin can result in the serious complication of pulmonary fibrosis. Bleomycin hydroxylase is an enzyme primarily responsible for degrading bleomycin and is present in all tissues except the lungs and skin, the key sites of the well-recognized pulmonary and skin toxicities.[6] The other leading hypothesis for pulmonary toxicity is the direct damage of vascular endothelium by bleomycin-induced cytokines and free radicals.[7]

The incidence of pulmonary toxicity (both asymptomatic, radiologic-only disease and symptomatic disease) is dose-dependent, occurring in 8.5% of patients exposed to $>$ 300 IU of bleomycin.[8] Bleomycin-induced pneumonitis (BIP) is associated with a mortality risk of 1% to 3%.[8,9] However, attempts to reduce or omit bleomycin in GCT treatment regimens have resulted in poorer survival outcomes.[6,10] Given that rates of grade 3 to 4 neutropenia approach 60% in patients receiving BEP,[10] granulocyte-colony stimulating factor (G-CSF) is often administered as both prophylaxis against febrile neutropenia and to maintain dose intensity. However, its use has been tempered by concerns over the potential association with BIP, as observed in Hodgkin lymphoma. The authors hypothesized that variations in the bleomycin hydroxylase gene may result in significant changes in bleomycin metabolism, though this was not formally explored in the study.[11]

Here, we report on a large single institution retrospective study examining the impact of G-CSF use on the incidence and severity of BIP. We also explored other potential risk factors for BIP development, as well as the degree of benefit G-CSF had on reducing rates of febrile neutropenia.

Patients and Methods

Our study used data collected as part of the Princess Margaret Cancer Centre institutional multi-disciplinary GCT database (eTestis). We identified all patients who received first-line chemotherapy for GCT between January 1, 2000 and December 31, 2010. From this group, patients who received BEP were then extracted for further analysis. In doing so, 2 patient populations were formed: the entire cohort and the bleomycin-treated cohort. The institutional practice during the study period was to use BEP as the predominant chemotherapy regimen for non-seminoma. For good-risk seminoma, 4 cycles of EP (etoposide and cisplatin) was the preferred institutional regimen up until 2008/2009, with a subsequent transition to 3 cycles of BEP.

The eTestis database was complemented by review of the pharmacy database to determine the specific chemotherapy regimens prescribed, as well as the use of G-CSF. BIP and febrile neutropenia events were identified by chart review of electronic medical records, including chest x-ray (CXR) and computed tomography (CT) scan reports. Information pertaining to the specific time point when BIP was diagnosed in relation to chemotherapy administration (during chemotherapy vs. after completion of chemotherapy) was not collected. Data extracted for this study included patient and treatment factors known to influence risk of developing BIP, including age, cumulative bleomycin dose received, presence of renal impairment, history of underlying lung disease including the presence of lung metastases (as this may influence pulmonary function test indices), and smoking history. GCT prognostic factors were also collected, including histologic subtype, primary site, IGCCCG risk category, and stage. Data on pulmonary function test indices were not readily available, as institutional practice did not mandate routine testing, in part owing to controversy surrounding its utility in detecting clinically significant BIP. Our study was approved by the local institutional Research Ethics Committee.

For the purposes of this study, definitions of key data points were predefined:

- G-CSF use was defined as at least 1 dose of filgrastim or peg-filgrastim received during the course of chemotherapy;
- BIP was defined as the presence of radiologic features consistent with pneumonitis within 90 days of bleomycin administration, without clinical, laboratory, or radiologic features that suggest concurrent infection. These radiologic features were assessed formally by radiologists, and reported as findings such as "ground glass opacities," "fibrosis," and other closely related terms. A similar approach to defining BIP has previously been utilized.[8] Pneumonitis was graded through retrospective chart review according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.
- Frequency of pulmonary radiologic evaluation: routine CXR/CT was not performed in asymptomatic individuals during chemotherapy administration. Following the completion of chemotherapy, imaging was routinely performed as part of local institutional guidelines for active surveillance. This involved CT abdomen/pelvis $\pm$ CT chest/CXR approximately 4 to 6 weeks post chemotherapy completion, and then the same imaging every 3 to 6 monthly intervals thereafter, depending on if retroperitoneal lymph node dissection was performed.
- Renal impairment was defined as at least 1 occurrence of creatinine clearance (CrCl) $<$ 80 mL/min (as measured by the Cockcroft-Gault formula) during the chemotherapy course. The cut-off of 80 mL/min was selected based on prior publications suggesting an increased risk of BIP at this degree of renal impairment.[8]
- Febrile neutropenia was defined as at least 1 occurrence of sustained temperature of $\geq$ 38°C for more than an hour, with an absolute neutrophil count of $<$ 1000/mm^3 (in accordance with CTCAE, version 4.0). Subsequent episodes of recurrent febrile neutropenia were not regarded as separate events; therefore, data pertaining to instances of febrile neutropenia despite G-CSF administration were not captured.

Statistical Analyses

We used SPSS version 21.0 (SPSS Inc, Chicago IL) for statistical analyses. Analyses were restricted to the cohort of patients that had been treated with bleomycin-containing chemotherapy regimens. Data were presented descriptively as means, medians, and their respective ranges. Analyses were conducted initially in the univariable setting with any variable showing a *P*-value of $<$ .10 being selected for further assessment in multivariable analyses.

We conducted univariable and multivariable analyses using logistic regression, to determine if there was an association between