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Original Article

Bleomycin-Induced Pulmonary Toxicity in Cancer Patients Treated at Tertiary Care Hospital

Aamira Ali, Faisal Mehmood*, Huma Ashraf*, Muhammad Umair Tufail, Amna Ashraf*, Syed Fawad Mashhadi**

Department of Medicine, Combined Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan, *Department of Medicine, Combined Military Hospital, Lahore/National University of Medical Sciences (NUMS) Pakistan, **Department of Community Medicine, Army Medical College/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To report the frequency of Bleomycin-induced pulmonary toxicity in cancer patients treated with chemotherapy regimens containing Bleomycin at Combined Military Hospital, Rawalpindi Pakistan.

Study Design: Case series.

Place and Duration of Study: Combined Military Hospital, Rawalpindi Pakistan, from Jan 2018 to May 2019.

Methodology: A total of one hundred and three (n=103) diagnosed cases of germ cell tumours and Hodgkin's lymphoma who were candidates of Bleomycin-based regimen aged 18-65 years were enrolled in the study. Bleomycin toxicity was assessed after four cycles of Bleomycin-based therapy.

Results: Bleomycin toxicity was observed in 24.3% (n=25/103) of patients in our study. No significant difference was observed in toxicity for age, gender, and cancer type (p>0.05 in all cases). Toxicity was observed in a significantly higher number of patients with smoking history as compared to non-smokers (64% vs. 36% p=0.001).

Conclusion: A significant percentage of patients who were on Bleomycin-based chemotherapy experienced Bleomycin-related toxicity, which was observed in a significantly higher number of patients with a smoking history as compared to non-smokers.

Keywords: Bleomycin, Germ cell tumours, Hodgkin's lymphoma, Pulmonary toxicity, smoking.

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INTRODUCTION

Bleomycin is a polypeptide antibiotic antineoplastic agent with broad activity & low myelotoxicity, making it an important component of chemotherapy regimens for curable cancers.[1,2] The major limitation of Bleomycin therapy is the potential life-threatening pulmonary toxicity, which occurs in 3-18% of treated patients.[3,4] Bleomycin is associated with subacute progressive pulmonary fibrosis, hypersensitivity pneumonitis, organizing pneumonia and acute chest pain syndrome during rapid infusion.[5] The likely mechanism of Bleomycin-induced lung injury includes components of oxidative damage, a relative deficiency of the deactivating enzyme Bleomycin hydrolase, genetic susceptibility, and elaboration of inflammatory cytokines.[6]

The potential for Bleomycin-related pulmonary toxicity has been appreciated for many decades. However, the scope of the problem is not well documented for Pakistani patients.[7] It is essential to report data on Bleomycin toxicity for future research formulating Bleomycin-based drug regimens focused on cancer treatment for the Pakistani population. The available data on incidence comes predominantly from international studies reporting patients treated with a Bleomycin-containing regimen for a testicular or ovarian germ cell tumour, ovarian sex cord-stromal tumour, or Hodgkin lymphoma.[8,9] The risk of Bleomycin-induced lung toxicity appears to be higher in older patients, smokers, and those with renal insufficiency. Thoracic irradiation and concurrent administration of Cisplatin at high doses may increase the risk of pulmonary toxicity.[10]

Despite its broad coverage of cancers and low risk of myelotoxicity, the major limitation of Bleomycin use in cancer treatment remains its associated pulmonary toxicity. The data regarding Bleomycin-induced pulmonary toxicity is scarce in the Pakistani population. The study aims to report the frequency of Bleomycin-induced pulmonary toxicity in cancer patients treated with chemotherapy regimens containing Bleomycin at CMH, Rawalpindi Pakistan.

METHODOLOGY

The case series was carried out at the Department of Oncology, CMH, Rawalpindi, from January 2018 to May 2019 after approval from the Ethical Review Committee (Dated 10 March 2017). The sample size was calculated using the WHO sample size calculator, taking a confidence level of 95% proportion of germ

Correspondence: Dr Amna Ashraf, Department of Medicine, Combined Military Hospital, Lahore Pakistan

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cell tumours and Hodgkin's lymphoma treated with Bleomycin who developed pulmonary toxicity of 22%.[11]

Inclusion Criteria: All diagnosed cases of germ cell tumours and Hodgkin's lymphoma who were candidates for a Bleomycin-based regimen, aged 18-65 years were included.

Exclusion Criteria: Patients with a history of chronic lung disease, chronic kidney disease, and radiotherapy of the lungs or thoracic region were excluded from the study.

Non-probability consecutive sampling was employed. Informed written consent was taken from the patients. Patients who were undergoing Bleomycin therapy for the treatment of cancer and fulfilling the inclusion criteria were included in the study. Patients who were on ABVD regimen for Hodgkin's lymphoma (Doxorubicin 25 mg/m2 IV bolus Days 1 and 15, Bleomycin 10 mg/m2 IV Days 1 and 15, Vinblastine 6 mg/m2 IV Days 1 and 15 and Dacarbazine 375 mg/m2 IV Days 1 and 15) and who were on BEP regimen (Bleomycin 30mg Days 1,8 and 15, Etoposide 100 mg/m^2 Days 1–5 and Cisplatin 20 mg/m^2 Days 1–5) were enrolled, given these regimens are widely accepted in the literature.[12,13] History taking and physical examination were performed by the trainee researcher. Bleomycin-induced toxicity was assessed after four cycles of either of the regimens as per our operational definition. Pulmonary toxicity was diagnosed on the presence of pulmonary symptoms (dyspnea and cough), bilateral interstitial infiltrates on chest x-ray, and high resolution computed tomography (HRCT) where needed, i.e. no remarkable findings on chest x-ray in the presence of symptoms and absence of clinical signs and symptoms of infection, e.g. no fever or total leucocyte within normal range.[14] The researcher conducted all the data collection to maintain data quality and compliance with the study protocol. All the gathered information was entered in the proforma.

Statistical Package for Social Sciences (SPSS) version 25.0 was used for the data analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. Chi-square test was applied to explore the inferential statistics. The *p*-value lower than or up to 0.05 was considered as significant.

RESULTS

A total of one hundred and three (n=103) diagnosed cases of germ cell tumours and Hodgkin's lymphoma of both genders who were candidates of Bleomycin-based regimen between ages 18-65 years were enrolled in our study. Gender distribution, distributions of different cancer types and smoking history are tabulated in Table-I. The mean age of participants is 45.40±15.61 years, with the mean age of males equal to 44.87±15.40 years and females equal to 47.17±15.61 years. Bleomycin toxicity was observed in 25(24.3%) patients. No significant difference was observed in toxicity for age, gender, and cancer type (p>0.05 in all cases). Toxicity was observed in a significantly higher number of patients with a smoking history as compared to non-smokers (64-36% p=0.001) (Table-II).

Table-I: Demographics Characteristics of the Patients (n=103)

Characteristics		Frequency(%)
Gender	Female	24(23.3%)
	Male	79(76.7%)
Age Groups	18-50 years	48(46.6%)
	51-65 years	55(53.4%)
Cancer type	Hodgkin's Lymphoma	70(68.0%)
	Germ cell tumour	33(32.0%)
Smoking history	Present	23(22.3%
	Absent	80(77.7%)
Bleomycin toxicity	Present	25(24.3%)
	Absent	78(75.5%)

Table-II: Comparison of Bleomycin Toxicity (n=103)

Variables		Bleomycin Toxicity		Total (n)(%)	*p*-value
		Present(n)(%)	Absent(n)(%)		
Age Groups	18-50 years	11(44.0%)	37(47.4%)	48(46.6%)	0.764
	51-65 years	14(56.0%)	(52.6%)	55(53.4%)	
Gender	Male	21(84.0%)	58(74.4%)	79(76.7%)	0.321
	female	14(56.0%)	41(52.6%)	55(53.4%)	
Smoking History	Smoker	16(64.0%)	7(9.0%)	23(22.3%)	0.001
	Non-smoker	9(36.0%)	71(91.0%)	80(77.7%)	
Type of Tumor	Hodgkin lymphoma	18(72.0%)	52(66.7%)	70(68.0%)	0.619
	Germ cell tumor	7(28.0%)	26(33.3%)	33(32.0%)	

DISCUSSION

Bleomycin is commonly used in chemotherapy and is one of the key drugs in induction chemotherapy for Hodgkin's lymphoma and testicular cancer. It has the advantage of less myelotoxicity; however, its severe and potentially fatal pulmonary toxicity has limited its dose intensity. Several clinical trials have focused on eliminating Bleomycin from the regimen or reducing the Bleomycin dose for testicular cancer patients with good prognosis.[12-14] However, the results indicate that Bleomycin is still an essential component of induction chemotherapy when only three courses are administered.

One study showed that out of 46 patients, 10(22%) experienced Bleomycin pulmonary toxicity, comparable to 24.3% of patients experiencing Bleomycin-induced pulmonary toxicity in our study. There was an overall mortality of 4.3%(n=2; N=46), with significantly more deaths in the Bleomycin pulmonary toxicity group compared to the cohort that did not have Bleomycin pulmonary toxicity (20% versus 0%; p=0.043). The Bleomycin pulmonary toxicity group was significantly older than the cohort that did not have Bleomycin pulmonary toxicity (48 versus 34 years; p=0.017). Furthermore, Adriamycin, Bleomycin, Vinblastine, and Dacarbazine, as front-line chemotherapy, were found to have a trend towards increased risk of Bleomycin pulmonary toxicity (90% versus 56%; p=0.067; power=31%). There did not seem to be significant differences in smoking status (10% versus 14%; p>0.05) between the two study groups.[12] We did not find a significant difference among age groups in our study; however, Bleomycin toxicity was significantly higher among smokers as compared to non-smokers. Another study concluded that prevention from Bleomycin-related lung toxicity lies in avoiding Bleomycin in older patients.[15] We did not find any significant difference among age groups in our study.

Another concluded that Bleomycin-induced pulmonary toxicity is noteworthy lung toxicity as subsequent mortality ranges from 10-20% and shrinks survival rate in patients with highly curable malignant conditions.[16] Similarly, our study found high rates of pulmonary toxicity. Therefore, physicians are advised to be vigilant concerning pulmonary toxicity in patients taking Bleomycin in the Pakistani population. Another study reviewed a total of 137 patients' data. The median time-elapsed since diagnosis was 11 years (range: 2-30 years). The study concluded similar findings of significant pulmonary toxicity in patients taking Bleomycin with or without irradiation.[17] The number of ABVD cycles with consequential Bleomycin dose significantly correlated with the SGRQ total score in patients receiving ABVD plus chest irradiation (p=0.01). Scintigraphy results correlated with Bleomycin dose in patients receiving ABVD without chest irradiation (right side: p=0.099, left side: p=0.051). Chest irradiation did not significantly worsen pulmonary function. They concluded that an additive negative effect of chest irradiation was not confirmed as reflected in the literature; however, Bleomycin was associated with worsened pulmonary function.[18] Our study concludes similar findings of high rates of pulmonary toxicity among patients taking Bleomycin. However, the effect of additional chest irradiation was beyond the scope of our study, which is a limitation of our study. Additionally, our study utilizes descriptive case series methodology done in a single centre in Rawalpindi. It is essential to undertake randomized controlled trials done over multiple centres to develop more reliable and valid data for Pakistani patients who need to undertake Bleomycin-based chemotherapy for cancer treatment.

CONCLUSION

A significant percentage of patients who were on Bleomycin-based chemotherapy experienced Bleomycin-related toxicity, which was observed in a significantly higher number of patients with a smoking history as compared to non-smokers.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

AA: & FM: Conception, study design, drafting the manuscript, approval of the final version to be published.

HA: & MUT: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

AA: & SFM: Critical review, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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