ORIGINAL ARTICLE

BLEOMYCIN INDUCED PULMONARY TOXICITY IN PATIENTS WITH GERM CELL TUMOURS

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Background: Bleomycin is a cytotoxic drug used in treatment of Germ Cell Tumours (GCTs) and is associated with pulmonary toxicity. Bleomycin pulmonary toxicity (BPT) manifests predominantly as pulmonary fibrosis, organising pneumonia (OP) or Nonspecific Interstitial Pneumonitis (NSIP). Our objectives were to determine the incidence of BPT, describe the common HRCT patterns of pulmonary toxicity and to find out the correlation of variables (cumulative dose of bleomycin, age and glomerular filtration rate) with pulmonary toxicity. **Methods:** The study included the data of 96 patients from March 2006 to September 2008. All patients had histologically proven GCT and received bleomycin containing regimes. Variables age, GFR at the time of initial presentation along with cumulative dose of bleomycin at completion of chemotherapy or at the time of BPT were recorded. The High resolution CT chest (HRCT) of these patients was independently reviewed by two radiologists. Bleomycin toxicity was reported on the radiologic features of pulmonary fibrosis, OP or NSIP. **Results**: Fourteen patients (14.6%) developed BPT. Common patterns of BPT were, pulmonary fibrosis (5.2%), OP (5.2%) and NSIP (4.2%). Using the Univariate regression analysis there was significant relationship between BPT and age, cumulative bleomycin dose and initial GFR at the beginning of treatment. **Conclusions:** Because BPT can be progressive and fatal, early recognition is important. The diagnosis of pulmonary toxicity should be considered in any patient with new or progressive respiratory complaints. BPT can be difficult to diagnose; therefore, knowledge and understanding of radiologic manifestations of toxicity caused by Bleomycin are necessary for institution of appropriate treatment. There is increasing incidence of BPT with increasing age, cumulative dose and decreasing GFR.

Keywords: Bleomycin, Pulmonary toxicity, Germ cell tumours, HRCT

INTRODUCTION

Bleomycin was discovered by Umezewa *et al* in 1966 and was originally isolated from the fungus Streptomyces verticillus.[1] It is a polypeptide antibiotic antineoplastic agent. Bleomycin pulmonary toxicity (BPT) has been known since the early clinical trials in the 1960s.[2] It is widely used in chemotherapy regimes for squamous cell carcinomas, Hodgkin's and non-Hodgkin's lymphoma, and Germ cell tumours. The major lung injury patterns as complication of bleomycin administration are pulmonary fibrosis, OP and NSIP.[3] Bleomycin is excreted by kidneys with 70% of dose excreted in first 24 hours. When excretion is compromised by low GFR, the drug half life is increased leading to longer exposure of the lungs.[4] The central event in the development of bleomycin induced injury is endothelial damage of the lung vasculature due to bleomycin-induced cytokines and free radicals. The diagnosis is established by a combination of clinical symptoms, radiological features and pulmonary function test results, while other disorders resembling BPT have to be excluded.[5] The overall rate of bleomycin pulmonary toxicity is 10%; cases are fatal in 1–2%. The incidence of BPT increases exponentially once total cumulative doses exceed 400–500 mg/m^2. Sex alone is not an independent risk factor.[6–8] Age of the patients is also an established risk factor for the development of BPT. Elderly patients have an increased susceptibility to develop BPT, especially those more than 70 years.[9–11] Chest X-ray can be normal up to 10% of cases and CT chest is more sensitive modality in evaluation of BPT.[12] Bleomycin pulmonary toxicity can manifest as pulmonary fibrosis, OP or NSIP. HRCT findings of pulmonary fibrosis include coarse reticular pattern, architectural distortion, bronchiectasis and honeycombing.[13] Organising pneumonia can be a manifestation of BPT. Typical HRCT findings are poorly defined nodular areas of consolidation, centrilobular nodules, branching linear opacities and bronchial dilatation.[14,15] The NSIP has also been reported as manifestations of BPT. Early high-resolution CT scans may show only scattered or diffuse areas of ground-glass opacity, later, findings of fibrosis (traction bronchiectasis, honeycombing) predominate in a basal distribution.[16,17]

The objectives of this study were to determine the incidence of BPT, describe the common HRCT patterns of pulmonary toxicity and to find out correlation of variables (cumulative dose of bleomycin, age and glomerular filtration rate) with pulmonary toxicity.

MATERIAL AND METHODS

After approval from our IRB and scientific review committee the data of 96 patients from March 2006 to September 2008 was retrospectively reviewed. All these

patients had histologically proven GCT and received bleomycin containing chemotherapy regimes. Patients who did not receive chemotherapy were excluded from study. Paediatric age group was also excluded. The variables recorded were age, initial GFR at time of presentation and cumulative bleomycin dose both at completion of therapy and at development of BPT. All above patients were subjected to CT scans for staging work up and treatment response according to NCCN guide lines. Those patients who presented in clinics with shortness of breath (SOB), fever or haemoptysis and suspected to have BPT were referred for HRCT. These HRCTs were independently reviewed by two radiologists with experience of 15 years and 5 years in reading HRCT. The radiological diagnosis of BPT was given on typical features of fibrosis, OP or NSIP. Final diagnosis was made in Multi-disciplinary Conference (MDC), attended by consultant radiologist, pathologist, pulmonologist and oncologist, on the basis of clinical and radiological findings and after exclusion of other aetiologies of symptoms for example infections. Bleomycin was later omitted from chemotherapy.

All the variables were analysed by SPSS-14 and Univariate regression analysis was done.

RESULTS

Out of these 96 patients 82 patients (85.4%) were below 40 years of age and 14 patients (14.6%) were above 40. Histology in 75% of patients was non seminoma and in 25% seminoma. GFR in 78 (81%) of patients was above 80 ml/min and in 18 (18%) was below 80 ml/min. 14 patients (14.6%) developed BPT. Common patterns of BPT were, pulmonary fibrosis (5.2%), OP (5.2%) and NSIP (4.2%). Univariate regression statistical analysis showed statistically significant correlation between BPT, age (p<0.001), cumulative bleomycin dose and GFR (p<0.002) and GFR (p<0.001). Regarding cumulative dose variable the percentage frequency of BPT was 11%, 14% and 16% in 91–180, 181–270 and 271–361 mg/m^2 individual groups respectively. The percentages of BPT in age variable were 12% and 28% in below 40 and above 40 years respectively. GFR variable showed incidence of BPT as 27% in GFR <80 ml/min and 11.5% in GFR >80%. Results are summarised in Table-1.

Table-1: Results

Variable	BPT %
Total incidence	14.6%
Common HRCT patterns	
Pulmonary fibrosis	5.2
OP	5.2
NSIP	4.2
Age in years	
<40	12
>40	28
Cumulative dose mg/m^2	
0–90	0
91–180	11
180–270	14
271–360	16
GFR ml/min	
<80	27
>80	11.5

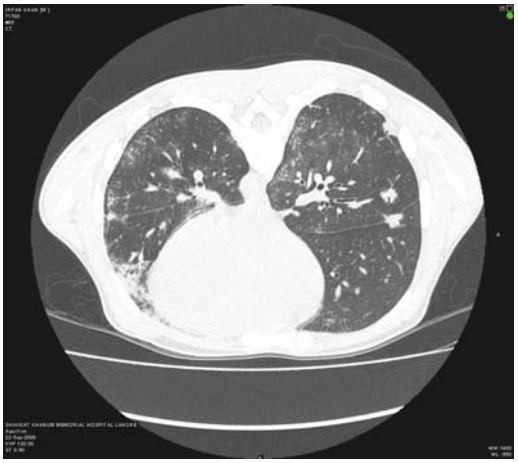

Figure-1: Bilateral ill defined pulmonary nodules with branching opacities consistent with OP

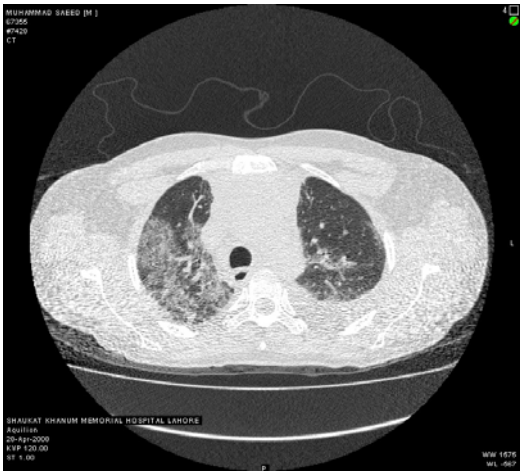

Figure-2: Ground-glass pattern more on right side with septal thickening, (NSIP)

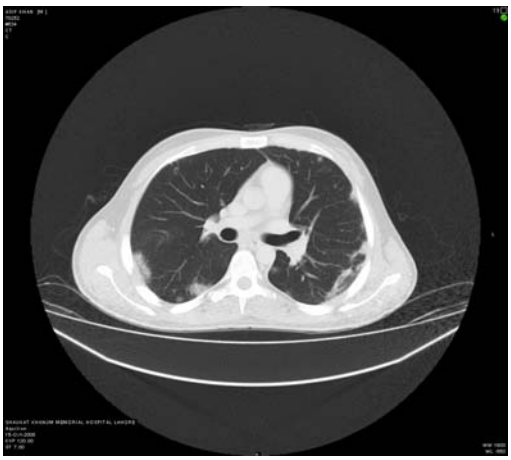

Figure-3: Bilateral subpleural fibrosis

DISCUSSION

The previous studies described incidence of BPT up to 10%.[3,6,7] Incidence in our study is greater than this (14.6%). The reason may be small sample and non

availability of DLCO facility.

We found that the commonest HRCT features of BPT were OP, NSIP and pulmonary fibrosis as also described by Sperber M.[3]

In our study the frequency of patients who developed BPT at cumulative doses of 91–180, 181–270 and 271–360 mg/m^2 was 11%, 14% and 16% respectively signifying increasing risk of BPT with increasing cumulative dose. Blum RH[2] reported toxicity in 5% and 17% at cumulative doses of bleomycin less than 400 mg/m^2 and more than 500 mg/m^2 respectively. Jules Elyse K[6] and Ali A[7] described that incidence of BPT increases exponentially as total cumulative doses approaches 400–500 mg/m^2. Our results also revealed similar patterns.

In our study the incidence of BPT in patients above 40 was more (28%) as compared to younger group (12%). Other studies by Blum RH[2], and O'Suliivan[12] also described the increasing risk of BPT with increasing age.

This study revealed increased incidence of BPT in patients with reduced GFR, 11.5% in patients with GFR >80 ml/min compared to 27% in patients with GFR <80 ml/min. This result is also consistent with O'Suliivan[12]

The sample volume of our study was less as compared to other studies. Probably this was the reason of higher incidence of BPT in our results. Our institution lacks the facility of DLCO. With combined usage of HRCT and DLCO there may be early detection of BPT and bleomycin can be omitted preventing the permanent damage to lung parenchyma.

CONCLUSIONS

Because BPT can be progressive and fatal, early recognition is important. The diagnosis of pulmonary toxicity should be considered in any patient with new or progressive respiratory complaints. BPT can be difficult to diagnose; therefore, knowledge and understanding of radiologic manifestations of toxicity caused by Bleomycin are necessary for institution of appropriate treatment and there are certain factors like age, cumulative dose and GFR that are associated with BPT.

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