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Original Research Article

Impact of the modified bleomycin, etoposide and cisplatinum chemotherapy regimen on the outcome of testicular germ cell tumor: a tertiary care institute experience

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ABSTRACT

Background: Bleomycin, cisplatin and etoposide (BEP) based combination chemotherapy is established as standard treatment for testicular germ cell tumors. As these tumors are highly curable, so management is crucial in terms of long-term toxicity particularly lung toxicity. With standard BEP there is increased toxicity which leads to poor compliance. So, we at a tertiary care center assessed modified BEP regimen in such patients and evaluated its effectiveness in terms of response and toxicity as compared to standard BEP.
Methods: Forty-nine patients of testicular germ cell tumors were enrolled in this study from January 2012 to December 2016. The modified BEP regimen consisted of bleomycin 30 IU day 1, cisplatin 20 mg/m^2 day 1-5 and etoposide 100 mg/m^2 day 1 to 5, given every three weeks. The planned drug intensities were 33.3 mg/m^2/week for cisplatin, 166.7 mg/m^2 week for etoposide and 10 IU/body/week for bleomycin. The schedule for chemotherapy was as follows: four courses of modified BEP for stage I patients and six courses of modified BEP for stage I S, II and III patients.
Results: Overall response rate in our study was seen to be 81.2% which was comparable with the available evidence. Five (10.4%) patients developed febrile neutropenia. Two (4.1%) patients showed clinically evident bleomycin induced pulmonary toxicity. Lower toxicity seen in these patients led to better overall compliance.
Conclusions: Modified BEP protocol is a good alternative to standard BEP with comparable efficacy and reduced toxicity.

Keywords: Testicular germ cell tumors, Febrile neutropenia, Modified BEP

INTRODUCTION

Over 95% of testicular cancers are germ cell tumors, either seminomas or nonseminomas. Seminomas are most commonly diagnosed between the ages of 30 and 34 years, whereas non-seminomas are usually diagnosed 5 to 10 years earlier. It has been found that roughly 8,300 new cases of testicular cancer are diagnosed annually in the United States, with 350 deaths.[1] Einhorn and Donohue have demonstrated that a combination of cisplatin, vinblastine and bleomycin was associated with 85% complete response rate.[1] The bleomycin, etoposide and cisplatin (BEP) regimen evolved from this original combination which had equivalent response and reduced morbidity.[2] Since then, bleomycin, cisplatin and etoposide (BEP) based chemotherapy is established as standard treatment for testicular cancers. With such good response rates, currently there are rising concerns regarding quality of life, cost-adequacy and patient compliance.

Several investigators are of the view that maintaining the relative dose intensity (RDI) of induction chemotherapy is important for optimal response.[3,4] In the study by Husband et al, increased average relative dose intensity (RDI) of cisplatin over the first seven courses did not correlate with improved survival.[3] However, patients who received a relative dose intensity of etoposide >0.75, 5 year survival was significantly improved compared with those in whom the RDI was <0.75 (79% vs. 44%, p<0.05), thereby suggesting that dose intensity of etoposide is an important determinant of outcome in the chemotherapy of metastatic non-seminomatous germ cell tumors (NSGCT). Similarly, the study by Miyanaga et al, suggested that the RDI of bleomycin might be one of the most important factors in achieving a chemotherapeutic effect from the PVB regimen.[4]

With the advent of new therapeutic modalities, there has been a remarkable progress in supportive care, such as administration of granulocyte colony-stimulating- factor (G-CSF) and 5-HT3 antagonists. It is important to know that the progress in supportive care has resulted in the improvement of the efficacy of BEP chemotherapy. However, data concerning the toxicity profile and completion of BEP treatment with the use of modern supportive care is scarce. So, with this background we planned to do a retrospective analysis of the detailed toxicity profile and completion of BEP chemotherapy for the patients treated at PGI Chandigarh, India between 2012 and 2016.

METHODS

Forty-eight patients of testicular tumors were enrolled in this study from January 2012 to December 2016. Of them, 43 patients were of non-seminomatous germ cell tumor (NSGCT) and 5 patients were of pure seminoma. The mean age at diagnosis was 30 years. Pretreatment staging consisted of physical examination, determination of serum tumor marker levels and radiological examination. The characteristics of the 48 patients are summarized in Table 1.

Treatment

All the patients underwent baseline investigative work-up which included: complete blood counts, biochemistry, serum tumor markers, chest and abdominal tomography. All the patients were assessed for high inguinal orchiectomy. The patients who were found to be inoperable at presentation were assessed for surgery after three cycles of BEP. Out of 48 patients, 40 underwent upfront high inguinal orchiectomy. According to TNM clinical staging, 1 patient was classified as stage I, 7 patients as stage I S, 17 patients as stage II and 23 patients as stage III. All patients received a modified BEP protocol consisting of bleomycin, etoposide and cisplatin as the chemotherapy. The schedule of BEP given is, 30 IU of bleomycin on day 1, 100 mg/m^2 of etoposide on days 1–5, 20 mg/m^2 of cisplatin on days 1-5, with recycling on day 22. Pegylated GCSF was given on day 6.[5] Therefore, the planned drug intensities were 33.3 mg/m^2/week for cisplatin, 166.7 mg/m^2/week for etoposide and 10 IU/body/week for bleomycin. To counter chemotherapy-related nausea, 5-HT3 antagonists were used in combination with dexamethasone and metoclopramide.

Table 1: Patient characteristics.

Median age	30 (16-64 years)
Histology	Non-seminomatous: seminomatous 43:5
Median BSA	1.7 (1.2:2.1)
Performance status	>70
Stage	N (%)
I	1 (2.08)
I S	7 (14.5)
II	17 (35.4)
III	23 (47.9)
Marital status	
Married	57%
Unmarried	43%
Smoking	N (%)
Smoker	15 (31.2)
Non-smoker	33 (68.7)
Alcohol	
Alcoholic	35 (72.9)
Non-alcoholic	15 (27.0)
Upfront surgery (high inguinal orchiectomy)	40 (83.3)
Scrotal violation	10 (20.8)

The chemotherapy schedule was as follows. Four courses of modified BEP for stage I patients and six courses of modified BEP for stage I S, II and III patients. In patients with disease progression a second-line chemotherapy most frequently used was paclitaxel, ifosfamide and cisplatin (TIP).[6] Patients underwent surgical resection of residual operable masses when all tumor makers were normalized by chemotherapy, but surgery was not performed for patients with adequately responding retroperitoneal lymph node (RPLN) mass (less than 3 cm in diameter in seminoma patients, and less than 1 cm in diameter in NSGCT patients without a teratomatous element). Tumor response was evaluated according to RECIST criteria v1.1. The patients were then followed up monthly for 1 year, bimonthly for the 2nd year, and at 3-month intervals for the 3rd year and semiannually thereafter using serum tumor markers, chest X-ray and abdominal ultrasonography.

Toxicity evaluation

The patient records were reviewed and the observed toxicities during the induction chemotherapy were graded according to CTCAE v4.0. Hematological toxicities and all episodes of dyselectrolytemia during chemotherapy were recorded. For post-chemotherapy pulmonary

function assessment, the diffusion capacity (DLCO) was measured by the single-breath method.

Relative dose intensity for BEP

The RDI of each drug was calculated by dividing the drug intensity actually given by the planned dose intensity and was expressed as a decimal with a value of 1.0 indicating that the patient received 100% of the planned dose.

Statistical analysis

The statistical analysis was performed using IBM SPSS software (version 23). The level of significance was set at $p<0.05$. Survival curves were constructed using the Kaplan–Meier method.

RESULTS

Completion and RDI of chemotherapy

Out of 48 evaluable patients, those with stage I S, II and III received six cycles of BEP and those with stage I received four cycles of BEP. The mean duration of chemotherapy was 4 months and 60% of the patients completed chemotherapy in overall treatment time. Chemotherapy cycles were delayed in 10 patients (20.8%) for 16 cycles which was due to chemotherapy related bone marrow suppression and patients' non-compliance. The delays in chemotherapy ranged from 7 to 21 days. The average delay was of 3 days. The RDI of the agents are listed in Table 2. The average RDI of bleomycin, etoposide and cisplatin was 0.35, 0.92 and 0.93**.**

Table 2: Relative dose intensity of modified BEP.

	Number of patients	%
Bleomycin		
>1.0-0.9	0	0
0.89-0.75	0	0
<0.75	48	100
Etoposide		
>1.0-0.9	27	56.25
0.89-0.75	12	25
<0.75	9	18.75
Cisplatin		
>1.0-0.9	26	54.17
0.89-0.75	11	22.92
<0.75	11	22.92

Toxicity

Hematologic toxicities

The most frequent toxicity was neutropenia. Neutropenia was seen in 30 (62.5%) patients. It was grade 2 in 38.7%, grade 3 in 6.12% and grade 4 in 4.08%. Other hematological toxicities included anemia and thrombocytopenia. Out of 30 patients, only five patients (10.4%) experienced neutropenic fever, all of whom were successfully treated with empiric broad-spectrum antibiotics. The incidence of neutropenia was maximum after the fourth (20.8%) cycle of chemotherapy. The median leucocyte nadir was in the range of 1200 per mm^3 to 1800 per mm^3 after three cycles of chemotherapy. The incidence and duration of neutropenia and neutropenic fever did not show any significant tendency. Thrombocytopenia resulting in the delay in treatment was seen in 7 (14.5%) patients. The 14 patients (21.1%) with hemoglobin levels below l0 g/dl were given red blood cell transfusions. Table 3 shows the details of hematologic toxicities.

Table 3: Toxicities.

	Grade 1 (n)	Grade 2 (n)	Grade 3 (n)	Grade 4 (n)
	N (%)	N (%)	N (%)	N (%)
Hematologic				
Neutropenia	6 (12.5)	19 (39.5)	3 (6.25)	2 (4.16)
Anemia	2 (4.16)	9 (18.75)	5	0
Thrombo-cytopenia	4 (8.33)	3 (6.25)	0	0
Neutropenic fever	Present		Absent	
	5 (10.4%)		43 (89.5%)	

n=number of patients.

Non-hematologic toxicity

The most common gastrointestinal toxicity was vomiting, which was of grade 1 in 22 patients (45.8%) and grade 2 in patients 7 patients (14.5%). Of other non-hematologic toxicities, electrolyte imbalance was observed. However, most of the imbalance was transient, which could be attributed to dehydration or vomiting during chemotherapy.

Pulmonary toxicity

The DLCO was measured after the last cycle of chemotherapy. So, DLCO was measured in all 48 patients after the completion of BEP. In our study only two (4.1%) patients showed clinically evident bleomycin induced pulmonary (BIP) toxicity during chemotherapy with hypoxia and fine crepitations. CECT chest revealed changes consistent with BIP. So, bleomycin was discontinued thereafter and patients received further cycles of EP.

Neurologic toxicity

In this study no clinically evident neuropathy was seen.

None of the patient had toxicity related death due to chemotherapy.

Response

Radiological response

Out of 48 evaluable patients, radiological complete response was seen in 16 (33.3%) patients, partial response in 23 (47.9%) patients, stable disease in 4 (8.3%) patients while 4 (8.3%) patients had radiological disease progression assessed after the last cycle of chemotherapy (Figure 1). The response was not known in one patient. Thus, the overall response rate was 81.2%. The CR rates were inversely proportional to the stage of the disease. The CR was achieved in 3 (6.25%) patients in stage III disease, 5 (10.4%) patients in stage II, 8 (16.6%) patients in stage I.

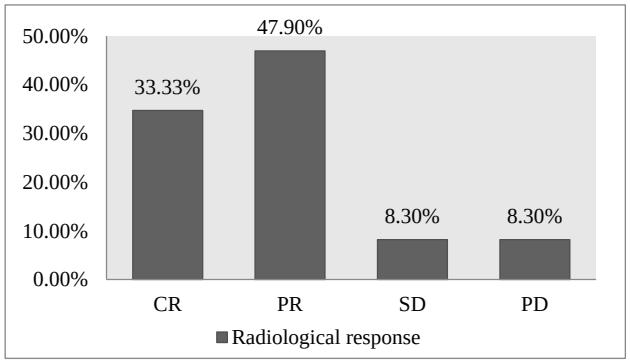

Figure 1: Radiological response.

Biochemical response

The complete biochemical response was seen in 35 (72.9%) patients, partial response in 8 (16.6%) patients while progression was seen in only 1 (2.1%) patient (Figure 2). The disease was stable in 4 (8.3%) patients. The CR was achieved in 16 (33.3%) patients in stage III disease, 12 (25%) patients in stage II, 7 (14.5%) patients in stage I.

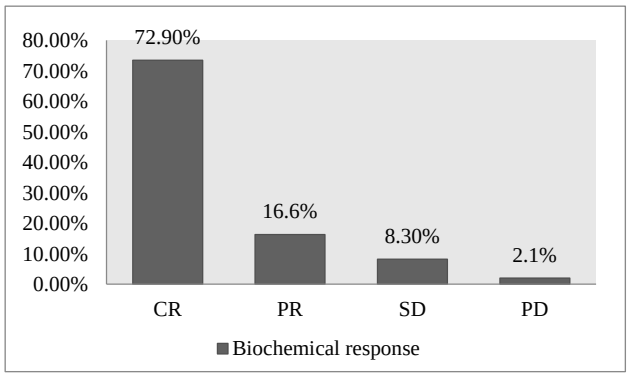

Figure 2: Biochemical response.

Relapse

10 (20.8%) patients had disease progression during follow up. Among the 16 patients (33.3%) who achieved both radiological and biochemical CR, only one patient (2.1%) relapsed whereas out of 23 patients with partial response, 6 patients (12.5%) relapsed and the differences were statistically significant (p=0.001). The serum tumor markers were also consistent with disease progression. On radiological findings, visceral relapse was found in 7 (14.5%) patients and nodal relapse in 2 (4.1%). 1 (2.1%) patient was found to have bony metastasis while 2 (4.1%) patients relapsed in the brain. Lung was the most common site of relapse accounting for 8.33% of the total patients. In addition to primary chemotherapy, second-line or salvage chemotherapy was required in only 3 patients (6.25%) for refractory or relapsed disease. TIP based chemotherapy was given in such patients.

PFS and DFS

The overall 2 year DFS and PFS were 71% and 85% respectively (Figure 3 and 4). The 2 year OS was 100% irrespective of stage. No significant correlation was found between the RDI of the individual drugs with OS and DFS. The 2 year DFS of patients with RDI of etoposide greater than 0.75 and below 0.75 was 71.7% and 66.6% respectively (p=0.831). The 2 year DFS of patients with RDI of cisplatin greater than 0.75 and below 0.75 was 72.2% and 66.6% respectively (p=0.124). The 2 year DFS for stage I, stage I S, stage II and stage III was 100%, 100%, 70.5% and 60.8% respectively.

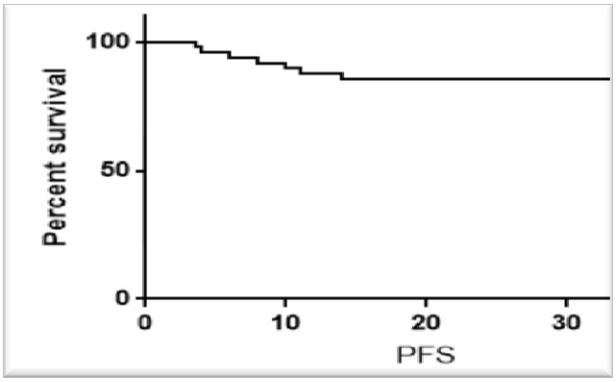

Figure 3: Progression free survival.

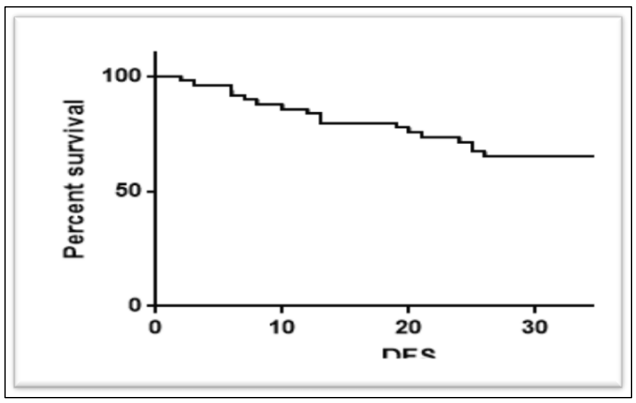

Figure 4: Disease free survival.

Status at last follow-up

The median follow-up period was of 38 months. Out of 48 evaluable patients, 30 (62.5%) patients had no evidence of disease at last follow-up. Out of these 30 patients, 15 patients had partial response after the completion chemotherapy. 3 (6.25%) patients had partial response, 3 (6.25%) patients had stable disease, 10 (20.8%) patients had the disease progression, 1 (2.0%) patient had recurrence while the status was unknown in one patient at the last follow-up. 16 patients achieved both radiological and biochemical CR after last chemotherapy. Out of these 16 patients, only one (2.0%) patient had relapse. Rest of the fifteen had no evidence of disease at last follow-up.

DISCUSSION

As the studies have shown more than 80% cure rates in both seminomatous and non-seminomatous testicular cancer with BEP, it is important to optimize the standard regimen and combining the benefits of maximal efficacy with minimal toxicity. The aim of our study was to achieve reductions in toxicity and inconvenience of therapy without affecting the efficacy.

The complete response rates and partial response in our study were 33.3% and 47.9% respectively and thus the overall response rate was 81.2%. In GETUG T93BP, 257 patients received either three cycles of BEP or four cycles of EP every 3 weeks. Patients were retrospectively stratified into the risk groups as per International Germ Cell Cancer Collaborative Group (IGCCCG) classification. Median follow-up period was 53 months. Favorable response after chemotherapy alone or post-chemotherapy surgery was observed in 124 patients allocated to three cycles of 3BEP (94.7%) and in 122 patients allocated to four cycles of 4EP (96.8%) (p=0.34). The 4-year event-free survival rates were 91% and 86%, respectively (p=0.135).

In a randomized phase III study by Nichols et al, 304 men with advanced disseminated germ cell tumors were randomly assigned to receive four courses of BEP or VIP. 299 patients were evaluated for toxicity and 286 for response. Overall complete remission rate (VIP, 37%; BEP, 31%), favorable response rate (VIP, 63%; BEP, 60%), failure-free at 2 years (VIP, 64%; BEP, 60%), and 2-year overall survival (VIP, 74%; BEP, 71%) were not significantly different between the two treatments.

In a study by Kantoff et al, an overall complete response rate of 82% was achieved with the rate of complete responses with conventional 5-day regimen chemotherapy of 60% and 22% with resection of the residual tumor masses.[7] In our series, the results were equivalent with a complete response rate of 81.2%. Similarly, in a study by Oliver et al comparable results were achieved by a modified regimen combining etoposide, bleomycin, and cisplatin given over 3 days as compared with the standard 5-day course in an adjuvant setting.[8]

The febrile neutropenia with our modified regimen was seen in just 5 patients accounting to 10.4% of all the patients. The delays in the chemotherapy were seen in just 10 patients (20.8%). The incidence of neutropenia became more marked after the fourth cycle of chemotherapy. In the study by Dearnaley et al, toxicity progressively increased with later courses of chemotherapy, with grade 3 toxicity occurring in 12%, 13%, 22.5% and 34.5%, respectively, in courses 1, 2, 3 and 4. In GETUG T93BP, the rate of neutropenia was 72% and 90% in 3BEP and 4EP arm respectively while the rates of febrile neutropenia were 7% and 5% in 3BEP and 4EP arm respectively. Grade 3-4 neutropenia was seen in 47% of patients in GETUG trial. The rates of grade 3-4 neutropenia in our study were 10.4%.

The incidence of pulmonary toxicity in our study was 4.1%. The average dose of bleomycin in our study was 166.7 IU. Bleomycin is an essential component of chemotherapy for testicular cancer but the major concern of its use is pulmonary toxicity and is the leading cause of treatment-related death of BEP.[10] The reported incidence of fatal Bleomycin induced pulmonary toxicity (BIP) is 0.8–2.8%.[9,10] The risk of BIP correlates directly to the cumulative bleomycin dose.[12] Recent studies have shown a strong correlation of BIP with impaired renal function and higher age.[11-13] In a study by Simpson et al, incidence of fatal BIP was 10% with a mean cumulative bleomycin dose of 180–210 mg, in testicular cancer patients over 40 years of age.[11] In our study the pulmonary toxicity was significantly less which might be due to the reduced cumulative dose of bleomycin in our patients. Instead of administering weekly doses of Bleomycin, we used Bleomycin only on day 1 of every chemotherapy cycle. This alternative approach really needs to be investigated keeping in view the significantly reduced toxicities and comparable efficacy. Additionally, the shorter hospital stay and the reduced number of infusions resulted in better compliance of the patients and gave them strength to adapt to the stress of chemotherapy. Thus, the patients' quality of life improved.

The average RDI of bleomycin, etoposide and cisplatin in our study was 0.35, 0.92 and 0.93. The dose intensity (DI) is defined as the amount of a given drug per unit of time. The relative dose intensity (RDI) is the fraction of a drug given, relative to the standard. The RDI can be calculated for each single agent or averaged over all the drugs in a combination regimen.[14] The DI is expressed in mg/m^2/week. The studies have shown a strong role of RDI but its distinct importance in the treatment outcome has not been demonstrated.[3,4] In the study by Husband et al, increased average relative dose intensity (RDI) of cisplatin over the first seven courses did not correlate with improved survival. However, patients who received a relative dose intensity of etoposide >0.75, 5 year

survival was significantly improved compared with those in whom the RDI was <0.75 (79% vs. 44%, p<0.05).[3] In our study RDI of bleomycin was lower but it did not put significant impact on PFS and DFS as it was effectively compensated for by the more number of cycles. Moreover, our modified BEP regimen resulted in far less pulmonary toxicity. So, to avoid fatal bleomycin toxicity, an alternative approach with our modified BEP regimen needs to be validated in further randomized trials.

CONCLUSION

The overall response rate was 81% which was comparable with the available evidences. The incidence of grade 3 and 4 neutropenia as well as febrile neutropenia was significantly less. There was no significant pulmonary toxicity and neurotoxicity. Hence, we strongly believe that modified BEP protocol is a good alternative to standard BEP regimen as it has comparable efficacy, reduced toxicity and better patient compliance and quality of life. However, as the sample size was very small, larger studies with longer follow-up need to be done to validate the results.

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