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The journal is official publication of the Association of Radiation Oncologists of India, and issues are published quarterly in the last week of March, June, September and December.

The Journal is printed on acid free paper.

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Journal of Cancer Research and Therapeutics

Journal of Cancer Research and Therapeutics

July-September 2007 | Volume 3 | Issue 3

CONTENTS

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Treatment outcome and cost-effectiveness analysis of two chemotherapeutic regimens (BEP vs. VIP) for poor-prognosis metastatic germ cell tumors

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ABSTRACT

Background: In patients with small-volume disseminated disease of germ cell tumors, cure can be achieved with four cycles of bleomycin, etoposide, and cisplatin (BEP). However, around 20% of these cases are not curable. Strategies to improve cure rates have shown that none of the currently available modalities were superior to the others. Among the most used ones, BEP and VIP (etoposide, cisplatin, and ifosfamide) have been the most studied. However, there are no reports comparing the two, except for a few in abstract forms from southern India. Therefore, we did a treatment outcome and cost-effectiveness analysis of two chemotherapeutic regimens (BEP vs VIP) that are used in poor-prognosis metastatic germ cell tumors.

Materials and Methods: All male patients with germ cell tumors, diagnosed as having poor risk by IGCCCG, between January 2002 and December 2004 were included in the study. Clinical, laboratory, and other data were recorded. The patients were stratified into two categories on the basis of the type of chemotherapeutic regimen they received.

Results: In all, 46 patients were analyzed, with a median follow up of 26.6 months. The baseline characteristics (age, stage, PS, histology, and serum markers) were not different in the two treatment arms. There is no significant difference in the outcome with either of the chemotherapeutic modalities. VIP is less cost effective and more toxic compared to BEP.

Conclusion: In view of the greater toxicity and cost of therapy, as well as lack of either overall or disease free survival advantage, VIP is not a preferred option for patients with high-risk germ cell tumors in the Indian setting and it is still advisable to treat patients with BEP.

KEY WORDS: Bleomycin, etoposide, and cisplatin, cost-effectiveness analysis, metastatic germ cell tumors, VIP

In patients with small-volume disseminated disease of germ cell tumors, cure can be achieved with four cycles of bleomycin, etoposide, and cisplatin (BEP). However upto 20% of the cases of the germ cell tumors are not curable.[1] In such cases, various attempts have been made to improve the outcome, e.g., by increasing the dose of cisplatin,[2] increasing schedule intensity,[3] or by adding more drugs/using alternative regimens.[4] Till date none of these measures have demonstrated any clear superiority over the conventional BEP regimen. However, in one of the recently conducted studies, etoposide, cisplatin, ifosfamide (VIP) showed better CR rates compared to the BEP regimen (37% vs 31%; though this was not statistically significant), and the authors concluded that there is more toxicity with VIP and it does not provide any clear survival advantage.[5] Though exact statistics are not available from all parts of India, the percentage of patients presenting in advanced disease is far more than the 20% reported in West. In view of the large number of cases presenting in the advanced stage (high-risk cases) in India, a resource poor nation, we undertook this retrospective analysis in patients receiving either BEP or VIP as first-line therapy to examine and compare the toxicity and cost effectiveness of these regimens.

MATERIALS AND METHODS

All male patients with germ cell tumors (high risk) attending the Kidwai Memorial Institute of Oncology (KMIO), Bangalore, between January 2002 and December 2004 were included in the study.
The inclusion criteria were:

1. Proven case of poor-risk germ cell tumor
2. Clinical, laboratory, and other details completely available
3. Minimum follow-up of 2 years after completion of therapy
4. Informed consent from the patient before any chemotherapy (a routine practice at our hospital)

The patients' clinical, laboratory, and other data were

collected from the records. The patients were stratified into two groups, depending on the type of chemotherapeutic regimen (BEP vs VIP) they received. Risk stratification and follow-up were done according to NCCN guidelines-2005. Out of the total of 52 diagnosed patients, complete details were available for 46 patients. While choosing the treatment modality, no fixed pattern was followed. However, in general, relatively young patients, with poor ECOG-Performance Status and having a higher tumor burden were allocated VIP and the others were allocated BEP. (For assessing tumor burden, no exact definition was followed; the decision was made by the treating oncologist based on the number of metastases or the levels of the serum markers). Cost of the therapy was calculated for all cycles of chemotherapy, including the management of complications. However cost for the follow-up and other investigations were not included, as we followed the same workup plan in both the treatment groups. Duration of hospital stay in both the groups included that for the chemotherapy administration and also any admission for management of complications. Each episode of grade 3 or 4 complication for each patient was calculated as a separate entity.

Statistical analysis

Mean cost of the therapy (as well as standard deviation) per patient was calculated in each group. Means were compared using the Student's t test and the differences, with 95% confidence interval (CI), were calculated for all parameters.

RESULTS

The mean age was 28.87 ± 7.19 (SD) years (range: 18-45). In all, 46 patients were eligible for analysis, with a median follow-up of 26.6 months. The baseline characters (age, stage, PS, histology, and serum markers) were not different in the two treatment arms and are represented in the Table 1. The response rates and the toxicity and the cost-effectiveness analysis in both the arms are presented in Tables 2-4, respectively.

Table 1: Baseline characters

Parameter	BEP (n = 27) Mean ± SD	VIP (n = 19) Mean ± SD
Age	33.8 ± 9.8	26.9 ± 6.6
Duration of symptoms (days)	65 ± 17	70 ± 22
IGCCCS risk category	100% high risk	100% high risk
Number of metastatic sites (average per patient)	1.8 ± 1.2	2.2 ± 1.6
Metastasis		
Lung	18	14
Liver	9	11
Nonregional lymphnodes	22	17
Serum markers (S1:2:3)	2: 3: 22	1: 2: 16
Histology		
Mixed elements	16	12
Choriocarcinoma	6	3
Yolk sac tumors	5	4

DISCUSSION

It has been proven in previous trials that there is no survival advantage gained by using VIP in place of the BEP in patients with high-risk germ cell tumors.[1,4,5] In one of the recently conducted MRC/EORTC trials, recruiting 380 patients, wherein BOP followed by VIP was compared to conventional BEP, the toxicity of the experimental arm was substantial, without providing any survival advantage.[4] In the EORTC trail comparing modified BEP with VIP, where 84 patients were studied, there is no difference in efficacy between the two regimens (CR: BEP 82% *vs* VIP 78%). However, grade 3/4 toxicities were more in those receiving VIP.[6] The results of the present study are not very different from other literature reports and reinforce the same. Though the CR rate is apparently higher with VIP, due to our small sample size we are not able to draw any conclusion regarding efficacy. On the whole, the recently reported trials in advanced poor-risk GCT suggest that a therapeutic plateau has been reached and it is unlikely that reconfiguration of currently available drugs will be able to improve outcomes.[5]

However we found that patients receiving VIP chemotherapy required less hospital stay than the patients receiving the BEP (30 *vs* 35 days; $P=0.05$). This is despite the fact that patients receiving VIP experience more episodes of grade 3 or 4 toxicities. The reason for this could be that patients require admission for a minimum of 7 days per course of BEP chemotherapy (admission is mandatory in most cases, even for giving bleomycin) compared to 5 days per cycle for VIP. The patients receiving BEP also required more number of hospital visits, requiring long travel and stay, compared to patients receiving VIP. Despite the cost involved in travel and the longer hospital stay, the cost of the therapy in the VIP group is significantly higher ($P=0.0001$), owing to the higher cost of the drugs and the greater number of complications.

It is also important to consider another fact: most of the patients in this group will have a relapse and we need to have an effective salvage treatment available. Current literature suggests that ifosfamide is one of the most promising single

Table 2: Treatment outcome in BEP vs VIP in patients with high risk GCT

Treatment	Complete remission	Partial remission	Progressive disease
BEP	12	9	6
VIP	13	4	2

Table 3: Cost-effectiveness analysis

Parameter	BEP (n = 27) Mean ± SD	VIP (n = 19) Mean ± SD	95% CI	*P*
Cost	45,120 ± 9018	60,910 ± 12026	7816 to 22138	0.0001
Duration of hospital stay	35 ± 7	30 ± 8	0.5 to 9.5	0.04
No. of episodes of toxicities	6 ± 3	12 ± 8	3 to 9	0.006

Table 4: Toxicity rates

Treatment	BEP (n = 27)	VIP (n = 19)
Anemia (grade III/IV)	12/9	9/4
Neutropenia (grade III/IV)	13/6	9/8
Thrombocytopenia (grade III/IV)	6/3	5/4
Febrile neutropenia (episodes)	8	14
Neuropathy	4	1
Others	3	2

chemotherapeutic agent in relapsed cases of GCT[7] and, therefore, it would be wise to keep this agent as a reserve; especially so since there is no survival advantage when it is used as a first-line agent.

In view of the absence of any survival advantage with VIP, and also because of the greater amount of toxicity and cost of therapy, it would be appropriate to treat patients of high-risk germ cell tumors with the conventional BEP rather than VIP in the Indian setting, keeping the latter regimen in reserve for the treatment of relapses.

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Source of Support: Nil, **Conflict of Interest:** None declared.