Journal of Cancer Research and Therapeutics

Nagragj Huilgol
Editor-in-Chief
Chief Radiation Oncologist,
Nanavati Hospital

Rajiv Sarin
Executive Editor
Director,
ACTREC

Consulting Editors

Hassan Awwad, Cairo, Egypt (Africa / Middle East)
Michael Brada, UK (London)
Minesh Mehta, Wisconsin, USA (America)
Yin Weibo, Beijing, China (Asia)
Kailash Narayan, Melbourne, Australia (Australia)
John Yarnold, London, UK (Europe)
GK Rath, New Delhi, India (AROI)
SK Shrivastava, Mumbai, India (ICRO)
Vikram Bhadrasain, National Cancer Inst (USA)
R Sankaranaranayan, IARC, Lyon (IARC)
Jens Overgaard, Aarhus, Denmark (ESTRO)

Consulting Editors - Specialties

Taisei Nomura, Osaka, Japan - (Cancer and Radiation Biology)
Rakesh Jalali, Mumbai, India - (Radiation Oncology (Clinical))
V Kannan, Mumbai, India - (Radiation Oncology (Technology))
Tharmar Ganesh, Delhi, India - (Radiation Physics)
Purvish Parikh, Mumbai, India - (Medical Oncology)
Rajan Badwe, Mumbai, India - (Surgical Oncology)
Van der Zee Cobi, Rotterdam, The Netherlands - (Hyperthermia)
Mhoira Leng, Scotland, UK - (Palliative Care)

Statistician
R Gurusamy, Mumbai, India

Editorial Board Members

Ahmed Mansoor, Kentucky, USA
A. K. Anand, Delhi, India
Billimaggia R, Bangalore, India
Buffalo ER, USA
Bulakova EB, Moscow, Russia
Chul Koo Cho, Seoul, Korea
Datta NR, Lucknow, India
Deshpande DD, Mumbai, India
Dinshaw K, Mumbai, India
Dwarakanath BS, Delhi, India
Dobrowski Werner, UK
Giri GV, Bangalore, India
Gupta T, Mumbai, India
Hurtwiz Mark, Massachusetts, USA
Kampinga HJ, AV Groningen, Netherlands
Kataria Tejinder, Delhi, India
Kaushal Vivek, Haryana, India
Kumarswamy, Bangalore, India
Kumar Shaleen, Lucknow, India
Lim Gerard, Kuala Lumpur, Malaysia
Manjunath N, Rosshindale, USA
Marotta F, Milano, Italy
Martinez Alvaro, MI, USA
M. Babaihah, Secunderabad, India
Mishra KP, Mumbai, India
Negi PS, Delhi, India
Ohnishi T, Nara, Japan
Patel F, Chandigarh, India
Pillai RK, Trivandrum, India
Prabir Kumar Sur, Kolkata, India
Raina V, Delhi, India
Rajan Bal, Trivandrum, India
Rao Koteswah, Manipal, India
Rana P. Singh, USA
Sathiyanaranayan VK, Mumbai, India
Sethi VK, Singapore
Sharma SC, Chandigarh, India
Sohartari Gondhowiardjo, Jakarta, Indonesia
Sathiyanaranayan VK, Mumbai, India
Kouloulis E Vassilis, Athens, Greece
Tokyo, Japan
Umadevi, Bhopal, India
Vidhyasagar MS, Manipal, India
Ye Xiong Li, Beijing, China
Nagathihalli S. Nagaraj, USA

OFFICIAL PUBLICATION OF THE ASSOCIATION OF RADIATION ONCOLOGISTS OF INDIA
CONTENTS

Editorial

Denying open access to published health-care research: WHO has the password?

Rajiv Sarin .................................................................133

Original Articles

Methods of intervention in reducing the psychosocial impact while dealing with cancer as a disease: A clinician’s point of view

S Trivedi, J Petera, S Fillip, Z Hrstka .................................................................135

On the transit dose from motorized wedge treatment in Equinox-80 telecobalt unit

Rajesh A Kinhikar, Sachin Patkar, Chandrashekhar M Tambe, Deepak D Deshpande ..................140

Salvage abdominal irradiation for refractory non-Hodgkin’s lymphoma

Riad Akoum, Emile Brihi, Michel Saade, Therese Hanna, Georges Chahine ................................143

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

Venkata Satya, Suresh Attili, Rama C Chandra, G Anupama, Loknath D, PP Bapsy, Hemant K Dadhich, Govind K Babu ..................................................................................150

Case Report

Synchronous dual malignancy: Successfully treated cases

Rashi Agrawal ..............................................................................................153

Review Article

Brain metastases from breast cancer: Management approach

Tabassum Wadasadawala, Sudeep Gupta, Vaishali Bagul, Namrata Patil ........................................157

Brief Communications

Can pomegranate prevent prostate cancer?

Melisa Pereira ..........................................................................................166

Serum total glutathione-s-transferase levels in oral cancer

Krishnananda Prabhu, Gopalakrishna P Bhat ..........................................................167

Transient asymptomatic bradycardia in patients on infusional 5-fluorouracil

K Talapatra, I Rajesh, B Rajesh, B Selvamani, J Subhashini ..................................................169

Synchronous malignancies of breast and thyroid gland: A case report and review of literature

Dwarka P Agarwal, Tej P Soni, Om P Sharma, Shantanu Sharma ........................................172

Book Review ..................................................................................................174

Scientific Abstracts ..........................................................................................175
Treatment outcome and cost-effectiveness analysis of two chemotherapeutic regimens (BEP vs. VIP) for poor-prognosis metastatic germ cell tumors

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, up to 20% of the cases of the germ cell tumors are not curable. In such cases, various attempts have been made to improve the outcome, e.g., by increasing the dose of cisplatin, increasing schedule intensity, or by adding more drugs/using alternative regimens. 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. 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.

**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 trial 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. 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.[6]

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

**Table 1: Baseline characters**

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

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Complete remission</th>
<th>Partial remission</th>
<th>Progressive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEP</td>
<td>12</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>VIP</td>
<td>13</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table 3: Cost-effectiveness analysis**
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.

REFERENCES


Table 4: Toxicity rates

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