Chemotherapy related toxicity in locally advanced non-small cell lung cancer

ABSTRACT

Background: For inoperable non-small cell lung cancer combined chemotherapy and radiotherapy plays an important role as a therapeutic modality. The aim of the present study was to analyze neoadjuvant chemotherapy related acute toxicity in locally advanced lung cancer (stage IIIA and IIIB) in Indian patients using Cisplatin and Etoposide combination chemotherapy.

Material and methods: Forty patients of locally advanced Non small cell lung cancer received three cycles neoadjuvant chemotherapy using Injection Cisplatin and Etoposide. The patients were taken for Radical radiotherapy to a dose of 60 Gray over 30 fractions in conventional fractionation after completing chemotherapy. Chemotherapy associated toxicity was assessed using common toxicity criteria (CTC v2.0)

Results: Forty patients were available for final evaluation. Median age of presentation of patients was fifty-six years. Thirteen patients had Non small cell lung cancer stage IIIA while twenty-seven patients had Stage IIIB disease. Anemia was the most common hematological toxicity observed (seen in 81% of patients). Nausea and vomiting were the most common non-hematological toxicity seen. Sensory neuropathy was seen in 38% of patients. 88% patients developed alopecia. Seven patients developed febrile neutropenia.

Conclusion: Neo-adjuvant chemotherapy using Cisplatin and Etoposide continues to be a basic regimen in the Indian set up despite availability of higher molecules, since it is cost effective, well tolerated and therapeutically effective. Blood transfusions, growth factors and supportive care can be used effectively to overcome toxicity associated with this regimen.

KEY WORDS: Lung cancer, chemotherapy, toxicity

INTRODUCTION

Locally advanced lung cancer is a challenge to the treating physician not only due to poor response to treatment but also due to treatment related morbidities. It is the leading site of cancer in males in three urban cancer registries of India. In males the AAR ranges from 1.36 – 15.55. Females show a lower incidence rate with AAR ranging from 0.98-4.40.[1] Cancer registries even in younger 20 –24 year age group have recorded cases of lung cancer but peak age specific rates are seen in seventh and eighth decade of life. Non-small cell lung cancer accounts for 75 – 80 % of all neoplasms of lung.[2] Majority of these patients are inoperable and constitute the locally advanced cancer group. These patients are potential candidates for systemic chemotherapy alone or along with radiotherapy.[3] They are usually managed by neoadjuvant chemotherapy followed by radiotherapy and treatment maybe associated with a variety of side effects.[4] One such Neoadjuvant chemotherapy regimen using Injection Cisplatin and Injection Etoposide has been used in trials due to its synergistic action.[5] Despite availability of higher molecules this regimen is useful since its therapeutic efficacy is proven and it is afforded by a majority of our patients coming from a poor socio economic strata.

Treatment related toxicities are a major concern as it often leads to interrupted treatments and poor quality of life for patients. The aim of this present study was to study the chemotoxicity profile in Indian patients on Cisplatin and Etoposide chemotherapy.

MATERIAL AND METHODS

Forty patients of Locally Advanced Non – small Cell Lung cancer were studied from January 2003 to December 2004 in this prospective trial. After history taking and clinical examination the patients underwent baseline investigations including complete haemogram and biochemistry profile. Chest X-Ray And CT scan evaluation was done. Bronchoscopic evaluation was done and biopsy taken. Mediastinoscopy evaluation of nodal status was done where indicated. CT scan of abdomen was done as part of metastatic work up. CT scan brain
was done where indicated. The Exclusion criteria included
[a] Age more than 70 years [b] KPS less than 60 [c] any prior
oncological treatment. [d] Co morbid conditions like diabetes,
cardiological problems and renal dysfunctions. The patients
received three cycles Neoadjuvant chemotherapy with
Injection Cisplatin and Injection Etoposide. Injection Cisplatin
was given in a dose of 100mg/m² in three divided doses from
day one to day three. Injection Etoposide was used in a dose
of 100mg/m²/day from day one to day three. The
chemotherapy cycles were repeated at three weekly intervals.
The patients were evaluated for Acute Toxicity of
chemotherapy twice a week. Common toxicity criteria (CTC
version 2.0) was used for toxicity grading. At the end of three
cycles of chemotherapy the patients were evaluated by repeat
CT scan of chest and abdomen and taken up for definitive
radiotherapy where indicated up to a dose of 60 Gray over 30
fractions in conventional fractionation.

RESULTS

The median age of presentation of patients in the study was
fifty-six years. There were thirty-two male and eight female
patients. Thirteen patients suffered from Non-small cell lung
cancer stage IIIA and twenty-seven patients had stage IIIB
disease. Squamous cell carcinoma was the most common
histology [78%]. 74% patients were smokers with a mean
duration of smoking of thirteen years. Cough and chest pain
were the most common presenting symptoms in 89% of
patients. All forty patients completed three cycles of
neoadjuvant chemotherapy and were available for evaluation.
The toxicity seen is tabulated in [Table 1].

Hematological toxicity: Anemia was the most common
hematological toxicity observed (81% of patients). At end of
second cycle of chemotherapy Grade 1 anemia was observed
in 39.4% of patients and 26.3% had grade 2 anemia. One
patient developed Grade 3 anemia. After third cycle of
chemotherapy, 40 % of patients developed grade 1 anemia
while 27% had grade 2 anemia. 13.5% patients had Grade 3
anemia.

After second cycle 27% patients developed Grade 1 leucopenia
while 18.9% patients had grade 2 leucopenia. At end of third
cycle Grade 1 leucopenia was seen in 38.8% of patients. 19.4%
had grade 2 leucopenia. Grade 3 leucopenia was seen in two
patients.

Grade 1 thrombocytopenia was seen in 13.8% of patients and
11.11% developed Grade 2 thrombocytopenia after second
cycle. At end of third cycle 44.44% patients had grade 1
thrombocytopenia while three patients had Grade 2
thrombocytopenia.

Gastrointestinal toxicity: Anorexia (Grade 1 and 2) was seen
in 52.7% of patients at end of third cycle. Grade 1 nausea
was seen in36.8% of at end of first cycle of chemotherapy. At
end of second cycle 54% patients had Grade 1 nausea while
40.5% had grade 2 nausea. 36.11% patients had grade 2
nausea at end of third cycle of chemotherapy. At end of first
cycle 47% of patients had Grade 1 and 2 vomiting. After
second cycle 48.6% had Grade 1 vomiting and Grade 2
vomiting was seen in 45 % patients. After third cycle 30.5%
had grade 1 vomiting while 41.6 % had grade 2 vomiting.

Neurological toxicity: Grade 1 sensory neuropathy was seen
in 33.3% of patients while two patients had Grade 2
neuropathy after third cycle of chemotherapy. Grade 1 or 2
anxiety was seen in 70% of patients while on treatment. Grade
1 and 2 depression was seen in 21.6% of patients. 32.4% of
patients had grade 1 depression after second cycle of
chemotherapy. At end of third cycle Grade 1 depression was
seen 13% of patients while Grade 2 depression was seen in
41.6%.

Renal Toxicity: Five patients developed Grade 1-2 increase in
creatinine level. No renal failures were observed.

Dermatological toxicity: 88 % of patients developed Grade
2 alopecia at end of third cycle of chemotherapy.

Constitutional toxicity: Grade 1 fatigue was seen in 51.35%

Table 1: Observed Chemotherapy Toxicity profile (N = 40)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Cycle I (%)</th>
<th>Cycle II (%)</th>
<th>Cycle III (%)</th>
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<tbody>
<tr>
<td></td>
<td>G1 G2 G3 G1</td>
<td>G2 G3 G1 G2 G3...</td>
<td></td>
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<tr>
<td>Anemia</td>
<td>- - - 39.4</td>
<td>26.3 - 40 27</td>
<td></td>
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<tr>
<td>Leucopenia</td>
<td>- - - 27</td>
<td>18.9 - 38.8 19.4</td>
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<tr>
<td>Thrombocytopenia</td>
<td>- - - 13.8</td>
<td>11.1 - 44.4</td>
<td></td>
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<tr>
<td>Anorexia</td>
<td>44 - 48</td>
<td>45.9 - 52.7</td>
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</tr>
<tr>
<td>Nausea</td>
<td>36.8 - 54</td>
<td>40.5 - 38.8 36.11</td>
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<tr>
<td>Vomiting</td>
<td>47 - 48.6 45</td>
<td>- 30.5 41.6</td>
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<tr>
<td>Sensory Neuropathy</td>
<td>- - - -</td>
<td>- - 33.3 -</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>21.6 - 32.4</td>
<td>- 13 41.66</td>
<td></td>
</tr>
<tr>
<td>Weight Loss</td>
<td>54 - - - -</td>
<td>21 - 33.3 63.88</td>
<td></td>
</tr>
<tr>
<td>Allergy</td>
<td>- - - -</td>
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<tr>
<td>Alopecia</td>
<td>88 % patients developed Grade 2 alopecia.</td>
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</tbody>
</table>

*Percentage of patients developing toxicity
†Grade of toxicity as per CTC v2.0
of patients while grade 2 was seen in 45.9% of patients.

54% experienced Grade 1 weight loss after first cycle while 21% had grade 2 weight loss after second cycle of chemotherapy. At the end of third cycle 33% had Grade 1 weight loss while 63.8% developed a Grade 2 weight loss.

**Febrile Neutropenias.** Seven patients had febrile neutropenias with no mortality.

No hepatotoxicity was observed nor were any allergic reactions noted.

Overall response was assessed using response evaluation criteria in solid tumors (RECIST). Two patients had complete response [5.26%]. Sixteen had partial response [40%]. Stable disease was observed in eleven patients [28.94%]. Progressive disease was seen in eleven patients. [28.94%]

**DISCUSSION**

The rationale of using neoadjuvant chemotherapy in locally advanced non-small cell lung cancer is to cause a decrease in the tumor bulk before instituting radiotherapy. A variety of chemotherapy related toxicity is observed in patients on such regimens. In our study we observed anemia in 81% of patients making it the most common hematological toxicity observed. The frequency of hematological toxicity increased from cycle one to cycle three. Grade 3 anemia was seen in 13.5% of patients after third cycle of chemotherapy. Jean Pujol et al observed Grade 3-4 anemia in 18% of patients treated by cisplatin, etoposide and ifosfamide. Leukopenia (Grade 1-3) was seen in 63.8% of our patients. Studies have shown an incidence of leukopenia up to 54%. We observed thrombocytopenia in 44.44% patients after third cycle of treatment. 97.2% of patients on treatment experienced nausea after second cycle of chemotherapy. Majority of these were Grade 1 nausea. Almost all patients experienced vomiting during second and third cycles of chemotherapy. Grade 1 vomiting was seen 48.6% of patients while grade 2 vomiting was seen in 45% of patients after second cycle of chemotherapy. Nausea and vomiting was seen despite standard antiemetic therapy. An incidence of Grade 1 vomiting of 21.4% to 28% has been observed in different studies. Sensory neuropathy was observed in 38% of patients after third cycle of chemotherapy. Out of these 33.3% of patients had grade 1 sensory neuropathy.

Albain et al observed grade 1 neurological toxicity in 21.42% of patients. Other studies have shown an incidence of 20.5% for sensory neuropathy. Five patients under study had a grade 1-2 increase in creatinine clearance. A 15 –23% incidence of grade 1 increase in creatinine clearance has been shown in various studies. No renal failures were observed in our study. Shepherd has observed that less than 10% patients achieve complete response to induction chemotherapy (range 0-23%). We observed a complete response in 5.26% patients.

Hematological toxicity were managed using blood transfusion, growth factors like Filgrastim 5mcg/kg, along with antibiotic support where indicated. Dose modification of chemotherapy may be needed in some of our patients due to poor chemotolerance. The above measures practiced judiciously were able to tide over most of the events quite effectively.

**CONCLUSIONS**

Treatment related toxicities not only cause limitation in quality of life of patients but also cause interruptions of the proposed therapeutic regimen. Hematological toxicity was the major concern using Cisplatin and Etoposide regimen. The toxicity is effectively controlled using conservative measures.

Cisplatin and Etoposide continue to be an effective regimen for treating locally advanced lung cancer in Indian patients.

**REFERENCES**