Chemotherapy Versus Best Supportive Care in the Management of Lung Cancer
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Abstract
This study was planned to evaluate the role of chemotherapy in improving survival in patients with inoperable lung cancer. Seventy eight patients with histologically proven lung cancer were followed up for a period of one year. Thirty eight out of them received chemotherapy and 40 patients received supportive care only. Main outcome measure was survival from the date of diagnosis. The patients receiving chemotherapy had a median survival of 23.2 weeks compared to that of 10.1 weeks in patients receiving best supportive care. Among patients with non-small cell lung cancer, median survival was 27.0 weeks in chemotherapy group and 10.3 weeks in supportive care group. Patients who received cisplatin plus docetaxel combination had a better survival than those who received MIC (mitomycin, ifosfamide, cisplatin) combination. Patients with good performance status benefited more from chemotherapy, although patients with poorer performance status also had significant improvement in survival with chemotherapy. In conclusion, chemotherapy results in a modest, but significant improvement in survival in patients with inoperable lung cancer compared to best supportive care alone.

INTRODUCTION
Lung cancer is one of the commonest malignant neoplasms all over the world. Worldwide more than half a million cases are diagnosed annually. It accounts for more cancer deaths than any other cancer. Most of the patients present with advanced disease, when curative treatments like surgery are not feasible. Untreated patients with advanced disease have a median survival of only a few weeks.

In recent years, there have been significant advances in the management of small cell lung cancer. Chemotherapy with the standard combination of cisplatin and etoposide, along with radiotherapy and prophylactic cranial irradiation where indicated has resulted in a median survival of 18-24 months in limited stage disease and 7-9 months in extensive stage disease, compared to a median survival of only 6-12 weeks in untreated patients.

The role of chemotherapy in advanced inoperable non-small cell lung cancer, however, continues to be a subject of debate. It is often considered ineffective or excessively toxic. However, meta-analyses have demonstrated that, compared to supportive care, chemotherapy results in improved survival in such patients. Studies have also shown that chemotherapy reduces symptoms and improves the quality of life. Recent years have seen the introduction of newer agents such as gemcitabine, vinorelbine, paclitaxel and docetaxel, and in combination with cisplatin they have given higher level of response, longer median survival and better side effect profile.

A previous study from this institute had reported a median survival of five weeks in untreated patients and 16 weeks for those receiving combination chemotherapy. A later study also reported improved survival with combination chemotherapy. In this study median survival for patients with non-small cell lung cancer (NSCLC) was 27.5 weeks whereas that for small cell lung cancer (SCLC) was 24.5 weeks. 30.5% of patients survived beyond one year and 11% beyond two years.

The present study is planned to evaluate the efficacy of chemotherapy in lung cancer compared to best supportive care only (including radiotherapy) and to study the factors that influence the survival of lung cancer patients.

MATERIAL AND METHODS
Eighty two patients with inoperable lung cancer who were treated at our institute during the period of January to June 2001 were included in the study.

They were divided into two groups based on the treatment they received. Group I (chemotherapy group) consisted of patients who received chemotherapy of any type routinely used at this Institute. In addition they also received best
supportive care only. Group II (best supportive care group) consisted of patients who received best supportive care only. Best supportive care was defined in this study as measured to improve quality of life of the patients through palliation of symptoms. This includes the use of radiotherapy in any form as and when indicated, and the use of non-cytotoxic drugs for symptom relief like painkiller, appetizers, iron, vitamin and protein supplementation and treatment of infection and as when needed.

A histological diagnosis was established in each case. Staging was done using appropriate investigations. Performance status of the patient was assessed at the time of enrollment into the study using Karnofsky performance status scale.\(^\text{11}\)

The patients were followed up for a period of one year from the date of diagnosis. Clinical and radiological assessments were made at 4 weeks intervals during the follow-up. The main outcome measure was survival. Survival time was calculated from the date of diagnosis.

### RESULTS

Out of the 82 patients, four patients were excluded as they did not attend follow-up after initial assessment. Among the rest, 38 patients received chemotherapy along with best supportive care (group I), and 40 patients received best supportive care only (group II). They were followed up for a period of one year or till their death, whichever was earlier. The detailed patient characteristics are presented in Table 1.

**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy Group I (n=38)</th>
<th>Best Supportive Care Group II (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (range)</td>
<td>56.95 (30-80)</td>
<td>55.05 (41-73)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>32 (84.2%)</td>
<td>37 (92.5%)</td>
</tr>
<tr>
<td>Female</td>
<td>6 (15.8%)</td>
<td>3 (7.5%)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSCLC</td>
<td>31 (81.6%)</td>
<td>36 (90%)</td>
</tr>
<tr>
<td>Squamous</td>
<td>17 (44.7%)</td>
<td>18 (45%)</td>
</tr>
<tr>
<td>Adeno</td>
<td>9 (23.7%)</td>
<td>8 (20%)</td>
</tr>
<tr>
<td>Large cell/poorly diff</td>
<td>5 (13.2%)</td>
<td>10 (25%)</td>
</tr>
<tr>
<td>SCLC</td>
<td>7 (18.4%)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III A</td>
<td>3 (7.9%)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>III B</td>
<td>21 (55.3%)</td>
<td>19 (47.5%)</td>
</tr>
<tr>
<td>IV</td>
<td>14 (36.8%)</td>
<td>17 (42.5%)</td>
</tr>
<tr>
<td>Performance status</td>
<td>83.16 ± 11.65</td>
<td>76.00 ± 10.08</td>
</tr>
<tr>
<td>(Karnofsky scale)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Both groups were comparable for age and sex. Histology and stage was not significantly different between the two groups. However, performance status score was significantly lower in the supportive care group (p=0.05).

Mitomycin C, ifosfamide and cisplatin (MIC) was the commonest regimen used - in 14 patients (36.8%) of NSCLC. Second commonest was cisplatin plus docetaxel in 11 patients (28.9%). Three patients received single agent vinorelbine, while two patients received cisplatin plus gemcitabine and one patient received gemcitabine alone.

Cisplatin plus etoposide was the commonest regimen employed in patients with small lung cancer - six out of seven patients who were enrolled in the study. The other patient with SCLC received etoposide, vincristine and ifosfamide.

Twenty four (63.2%) patients out of 38 received three or more cycles of chemotherapy. Fourteen patients (36.8%) received two or less cycles of chemotherapy.

None of the patients had a complete objective response to chemotherapy. Twelve patients (31.6%) had a partial objective response to chemotherapy as documented by radiology. Eight patients (21.1%) had stable disease which did not progress during the course of chemotherapy. Eighteen patients (47.3%) had progressive disease during chemotherapy.

Twenty one patients each in both chemotherapy group and supportive care group received thoracic radiotherapy. In the chemotherapy group, 12 patients (31.6%) had received multiple fractions radiotherapy (2000-3000 cGy), while nine (23.7%) received single fraction radiotherapy. In the best supportive care group, this was 14 (35%) and seven (17.5%) respectively.

Overall median survival when both groups were taken together was 12.4 weeks. Median survival in the chemotherapy group was 23.2 weeks and that in best supportive care group, it was 10.1 weeks. The difference was statistically significant (p<0.001, log rank test). Figure 1 shows the Kaplan-Meier survival curve of all patients. In the chemotherapy group, nine patients (23.7%) survived more than one year, while in the supportive care group only one patient (2.5%) survived more than one year. The number of patients surviving six months or more were 18 (47.4%) in the chemotherapy group and two (5%) in the supportive care group.

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**Fig 1: Kaplan-Meier survival distributions including all the patients according to study group [Chemotherapy vs. best supportive care (BSC)]**
Patients were divided into two groups based on their Karnofsky performance status score (KPSS). Group 1 had KPSS >80 and group 2 had a KPSS <80. In the chemotherapy group, 30 patients belonged to group 1 and eight patients belonged to group 2. In the best supportive care group, 19 patients belonged to group 1 and 21 patients belonged to group 2. Median survival for patients in group 1 was 30.0 weeks in chemotherapy group and 12.4 weeks in best supportive care group. In group 2 patients, this was 13.1 weeks and 6.7 weeks, respectively. The survival difference was significant in both the groups (p<0.05, log rank test).

In patients with non-small cell lung cancer, median survival was 10.3 weeks in BSC group and 27.0 weeks in the chemotherapy group. Survival difference between the two groups was statistically significant (p<0.001, log rank test). Figure 2 shows the Kaplan-Meier survival curve of NSCLC patients. One year survival was 25.8% (8 patients) in the chemotherapy group and 2.6% (1 patient) in supportive care group. When patients who received two cycles or less of chemotherapy were excluded from the analysis, the overall median survival was 41.1 weeks.

Survival was also assessed according to the chemotherapeutic regimen received by the patient. Median survival was more than one year (52 weeks) in the group of 11 patients who received cisplatin and docetaxel. Seven patients (63.6%) survived more than one year in this group. Median survival was only 15.1 weeks in patient who received MIC (Mitomycin C, ifosfamide and cisplatin) regimen. None of the patients survived more than one year. Difference in survival between the two groups was significant (p<0.0001, log rank test). Even after patients who received two cycles or less of chemotherapy were excluded from the analysis, median survival in MIC group was 23.0 weeks. In patients receiving other regimens (n = 6) median survival was 23.4 weeks, and one patient receiving single agent gemcitabine survived more than one year.

In patients with SCLC, seven patients received chemotherapy out of which six had extensive stage disease. Median survival was 15.6 weeks and one patient with extensive stage survived more than one year. Among four patients in the best supportive care group, all had extensive stage disease. Median survival was only 3.9 weeks.

**DISCUSSION**

This study was planned to evaluate efficacy of chemotherapy in advanced lung cancer in prolonging survival as compared to best supportive care and to study the factors involved. The study compared the patients who received chemotherapy with those who received best supportive care only, including radiotherapy. The main outcome measure was survival. Because of logistical reasons, follow-up period was limited to one year and hence survival data beyond one year is not included in the study.

Most of the lung cancer patients present at an advanced stage when treatment with curative intent is not possible. The introduction of combination chemotherapy has given the hope of prolonging survival in such patients. In small cell lung cancer, chemotherapy has shown definite improvement in survival. In our study, the number of patients with SCLC was small. Even though, the survival benefit was smaller than that noted in previous studies; a significant improvement was seen in patients who received chemotherapy compared to those who received supportive care only.

In NSCLC, studies comparing best supportive care with chemotherapy had consistently shown better survival in patients receiving chemotherapy. The meta-analysis by Non-small Cell Lung Cancer Collaborative Group had shown improvement in one year survival by 10% in those receiving chemotherapy compared to those receiving best supportive care only. Recent trials comparing chemotherapy using newer agents had noted a median survival of 6.2 to 7.5 months in patients receiving chemotherapy compared to 4.6 to 5.7 months survival in patients receiving best supportive care. The study by Anelli et al., in stage IV non-small cell lung cancer non-metastatic to the brain, noted a median survival 55 weeks in patients receiving chemotherapy compared to 23 weeks in patients receiving supportive care.

In our study also, significant improvement in survival in patients with NSCLC who received chemotherapy was noted. The survival benefit was more in patients with better performance status. However, even in patients with poorer performance status, improvement in survival with chemotherapy was statistically significant.

When individual chemotherapeutic regimens used in NSCLC were compared, cisplatin plus docetaxel gave much better results than MIC regimen. Median survival was greater than one year in patients who received the first regimen and
63.6% of the greater activity of this combination in NSCLC. Previous studies with cisplatin plus docetaxel had noted median survival of 7.4 to 12.8 months in treated patients.\textsuperscript{13,14,15}

MIC which is an older regimen had a poorer response in this study. Out of 14 patients who received it, none survived more than one year and median survival was 15.1 weeks. Even after excluding patients who received less than two cycles of chemotherapy, median survival was only 23.0 weeks. This was much lower than median survival of 7.5 to 9.2 months reported in previous studies.\textsuperscript{16,17,18}

Advanced lung cancer is a terminal disease and it is important that in extending survival the quality of life should remain acceptable. There has been concern among physicians regarding the toxicity of chemotherapeutic agents leading to poor quality of life, in return for small improvement in survival. Quality of life was not assessed in this study. Many of the recent trials comparing chemotherapy with best supportive care have incorporated a measure of quality of life. These studies have demonstrated that survival benefit obtained with chemotherapy is accompanied by improvements in various quality of life components, despite the occurrence of side-effects.\textsuperscript{19,20}

Prolongation of life, even for a few weeks is important because of many socioeconomic reasons. One can perform social obligations like marriage of children during this period. Some patients may be willing to suffer considerable toxicity in return for a small improvement in survival. Although chemotherapy is generally reserved for symptomatic patients with good performance status and limited weight loss, this study has shown that even patients with poor performance status can benefit from chemotherapy. The decision to start chemotherapy should be taken only after a thorough discussion with the patients and relatives regarding the pros and cons of therapy.

Survival advantage conferred by chemotherapy is at best, modest. Newer treatment modalities such as angiogenesis inhibitors, tumour cell enzyme inhibitors, gene therapy and immunotherapy are being developed with an aim to further improve the results.\textsuperscript{21} Smoking is the most important risk factor for lung cancer and stopping smoking can markedly reduce the incidence of this dreaded disease. It is therefore more important to take preventive measures against lung cancer by campaigns to avoid smoking and other known risk factors for this disease.

**REFERENCES**