High-dose Chemotherapy in Lung Cancer*

R. L. Souhami, M.D.

Although small cell lung cancer (SCLC) is a very chemosensitive tumor, the dismal long-term survival rates show that with current combination drug regimens, it is rarely chemo-curable. For the great majority of patients, the disease is disseminated at diagnosis, and any hope of a substantial increase in cure rates must lie in more effective systemic treatment. It is these considerations which have led to the exploration of the use of very high-dose drug treatment. There are now enough studies in SCLC to be able to make an assessment of the possible value of this approach. In non-small cell lung cancer, there are too few studies to pass comment, except to say that the difficulties are likely to be even greater in view of the relative insensitivity to chemotherapy of these histologic types.4

Not all drugs are suitable for use in high-dose regimens because, for some, the dose-limiting toxicity is not hematologic (which can be partially overcome by autologous bone marrow transplantation (ABMT). In SCLC the most active drugs for which it is possible to increase the dose significantly are cyclophosphamide (and some other alkylating agents of less certain activity such as melphalan), etoposide, and carboplatin. In the case of cyclophosphamide it is clear that an increase in dose to 200 mg/kg is associated with an increase in response in untreated patients, but the schedule of administration may be important, since considerably more activated drug is produced when the dose is divided over successive days. Similarly, Slevin5 has shown that the same total dose of etoposide produces responses in 79% of untreated patients when given in a 5-day schedule but in only 10% as a 24-h infusion.

Several studies have assessed the use of high dose chemotherapy as a "late intensification" treatment, by which is meant that a conventional drug regimen is used to induce a response and that responding patients are then treated with the intensive regimen. In designing such studies there are several important considerations:

1. Are the same drugs to be used for induction as for intensification? If so, the assumption is being made that tumor persistent after a few cycles of treatment will be sensitive to a single cycle of the same drugs at higher dose. If not, some effective agents must be kept for the intensive regimen, using for induction of initial response only those drugs which cannot be intensified and which are preferably of a different class. The results will then depend on the degree to which resistance to drugs of one class is accompanied by resistance to other unrelated agents.

2. How long should the period of induction treatment be continued? Clearly, tumor persistent after a long period of chemotherapy is less likely to respond to the intensification, and cumulative myelosuppression will increase the toxicity of the high-dose treatment.

3. Should only those patients where a complete response of the tumor is obtained be treated? If so, this will make the results of the intensification unassessable except by survival and will limit the use of the technique to a relatively small group of patients.

The advantages and limitations of the "late intensification" strategy are set out in Tables 1 and 2. Several studies have

---

Table 1—Advantages of Using High-dose Chemotherapy as "Late Intensification"

<table>
<thead>
<tr>
<th>Advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor mass is smaller</td>
</tr>
<tr>
<td>Tumors are selected as responding to chemotherapy</td>
</tr>
<tr>
<td>Marrow less likely to be involved</td>
</tr>
<tr>
<td>Only patients with a chance of long survival are treated</td>
</tr>
</tbody>
</table>

Table 2—Limitations of Using High-dose Chemotherapy as "Late Intensification"

<table>
<thead>
<tr>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreated, probably drug-resistant, residual tumor</td>
</tr>
<tr>
<td>Pretreated patient. Toxicity greater</td>
</tr>
<tr>
<td>No response assessment (in CR patients). Survival is end point.</td>
</tr>
<tr>
<td>Unless this is spectacular, there is an early need for randomized studies</td>
</tr>
</tbody>
</table>
---

*From the Department of Oncology, University College and Middlesex School of Medicine, The Courtauld Institute of Biochemistry, London, England.

---

19 Vogel SE, Mehta C. Standard (STD) vs Intensive (INT) induction chemotherapy of small cell bronchogenic carcinoma (SBBC) with cyclophosphamide (C), CCNU (C) and methotrexate (M), followed by continued CC/M or cyclic maintenance therapy—a randomized trial of the Eastern Cooperative Oncology Group. Proc AACR/ASCO 1981; 22:199

---

*Downloaded From: http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21597/ on 06/26/2017*
used this approach. In the study of Banham et al and Sculier et al, the same drugs were used for response induction and intensification. Although additional responses were seen, these were not durable or useful. Smith et al induced a response with 4 cycles of doxorubicin, etoposide, and vincristine, and then used high-dose cyclophosphamide (given as a single infusion) to intensify. Again, some complete responses were obtained by intensification in patients who had responded only partially to the initial chemotherapy, but the duration was brief (8-12 weeks) and not of clinical value.

Spitzer et al used 2 multiagent induction regimens in 10 and 22 patients and then intensified treatment using 2 cycles of relatively high-dose therapy including essentially the same drugs. This was followed by radiotherapy and maintenance chemotherapy, so that the contribution of the high-dose procedure cannot be independently assessed. The median survival of these 32 limited-disease patients was 14 months—similar to results from conventional therapy. The median survival in 13 complete responders was 23 months, with a few long-term (>4 years) survivors, but, in a selected series, this cannot be confidently attributed to the high-dose strategy.

The study of Humblet et al is of interest because after induction of response in 101 patients, 45 were randomized to a high-dose cycle (cyclophosphamide 6 g/m² over 4 days, etoposide 600 mg/m², BCNU 300 mg/m²) or the same drugs in a single cycle at conventional dose (750 mg/m², 600 mg/m², 60 mg/m², respectively). There was a slight increase in long-term survival in the higher-dose group, which was not significant statistically. Relapse-free survival was longer in the intensified group. This study shows that relapse-free survival is longer with the higher-dose cycle, but the size of the difference means that the clinical value is debatable. Nevertheless, this is the only study that systematically addresses the central question of the value of intensification. It must be noted that, in the high-dose treatment only the BCNU had not been used in the initial induction treatment, so it could be argued that a more striking result might be obtained with the same basic study design but using different drugs for initial and intensive treatments. High-dose chemotherapy has also been used as initial treatment. The potential advantages and disadvantages of this approach are listed in Tables 3 and 4. When patients with limited disease are treated with high-disadvantages dose chemotherapy followed by thoracic radiation, it is possible that results at least as good as conventional treatment might be obtained and a reliable assessment of response to dose increases can be made. We have shown that cyclophosphamide 160-200 mg/kg is associated with a response rate of 84%, but this is not increased by a second cycle. Similar high response rates can be achieved with etoposide or etoposide and cyclophosphamide. In all these studies median survival is no different from that which would be anticipated in the same patient population treated conventionally.

At present, high-dose chemotherapy program must be regarded as a form of clinical investigation. They have no proved advantage over conventional treatment. Future strategies for further development of this approach are outlined in Table 5. The aim of such studies must be a careful definition of drug dose and of the most effective drug combinations. More information will also be needed on which combinations can be regarded as partially non-cross resistant and on the optimum timing of intensification. Further randomized trials will then be required to show if this form of drug intensification has a substantial advantage over conventional treatment.

REFERENCES

2 Ruckdeschel JC, Finkelstein DM, Mason BA, Creech RH. Chemotherapy for metastatic non small cell bronchogenic carci-
3 Sonnami RL, Harper PG, Linch DC, et al. High dose cyclo-
4 Schuler V, Ehninger G, Wagner T. Repeated high-dose cyclo-
phosphamide administration in bone marrow transplantation: exposure to activated metabolites. Cancer Chemother Pharma-
col 1987; 20:248-252
5 Slevin M. Personal communication, 1988
Altered Fractionation for Non-Small Cell Carcinoma of the Lung

Rationale for the Prospective Trials of the Radiation Therapy Oncology Group


The size and frequency of individual treatments or "fractions" and the total dose administered are the most important decisions available to the radiation oncologist; they are equaled only by determination of the treatment volume. Fractionation regimens in common practice for cancer of the lung vary considerably from one nation to another, and among institutions within a country. Large fractions, eg, 3-6 Gy, and low total doses (30-40 Gy) are common when the primary aim is palliation; smaller-sized fractions, eg, 1.8-2.5 Gy and higher total doses (50-60 Gy) are common if longer survival is the aim.

Recently, better understanding of acute and late effects of radiations on normal tissues and appreciation of tumor cell kinetics during treatment have led to new enthusiasm for departures from common fractionation. "Altered fractionation" is, therefore, considered anew as a promising means to increase local-regional control and survival in cancer of the lung.

Prospective clinical trials of altered fractionation for cancer of the lung have been conducted by the Radiation Therapy Oncology Group (RTOG) for more than 15 years. Early trials in non-small cell carcinoma of the lung were aimed at the most cost effective palliation; they used large fractions and low total doses. The most important early study, however, investigated the question of dose response with 2.0 Gy per fraction. This study (RTOG Protocol 73-01) demonstrated a dose-response relationship for control of tumors within the irradiated volume1,2 for patients with inoperable, stage 3 (MO) non-small cell carcinomas. RTOG investigators entered nearly 500 patients into these early trials, which demonstrated a dose-response relationship not just for control within the irradiated volume but also for survival. As a result, the standard for RTOG studies of sensitizers, biologic response modifiers, and other adjuncts became 60 Gy in 30 fractions of 2.0 Gy in 6 weeks.

Laboratory and clinical data subsequently became available that suggested potential advantages of standard or smaller-sized fractions administered more often and/or with a smaller interval than 24 h between fractions.4 Hyperfractionation (HFX) uses smaller-sized fractions (than common fractionation), which permits an increase in total dose in the same amount of time as with standard fractionation, without a corresponding increase in late effects in normal tissues. Accelerated fractionation (AFX) uses common or standard fraction sizes given more frequently to deliver approximately the same total dose as standard, but in a much shorter time.

Recent data have suggested that accelerated proliferation or repopulation may occur in tumors in humans as well as laboratory animals, as a result of the triggering of more rapid division of surviving clonogens as the tumor shrinks following the first irradiation or other insult with any cytotoxic agent.5 While HFX and AFX both exploit reoxygenation from normal cells and may radiosensitive phases of the cell cycle and reoxegenation within tumors, HFX overcomes accelerated proliferation by an increase in total dose over the usual treatment time, and AFX avoids much of the accelerated proliferation by completing delivery of the total dose in a reduced period of time.

Recently, the RTOG has accrued nearly 1,000 patients to prospective trials seeking the upper limits of total dose with HFX.6 The most recent trial is termed "phase 1/2," but it differs profoundly from chemotherapy trials with similar apppellations by virtue of an emphasis on late effects end points.6 This type of evaluation requires that larger numbers of patients be entered into trials to have a sufficient sample of patients for an accurate assessment of late effects, at least at 12-18 months.

Five total doses have been studied with HFX, 60.0-79.2 Gy, delivered as 1.2 Gy twice daily, 10 fractions per week. These trials have been closed, and results are expected which will indicate the most effective total dose. AFX is being explored with three regimens using 1.8 Gy via concomitant boost: a large field is treated 5 times per week.