Dose-Intensive Therapy in Small Cell Lung Cancer*

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Basic to curative treatment for small cell lung cancer (SCLC) are the principles of dose response, combination chemotherapy, and combined-modality therapy. Theory and experimental and clinical data suggest that solid tumors recur, despite initially responding to chemotherapy due to drug resistance. Resistance to chemotherapy is potentially overcome by using 5- to 10-fold higher doses. To decrease the emergence of drug resistance, combinations of active non-cross-resistant agents are used. Hematopoietic stem cell support provides the opportunity to test dose response to the limits of organ tolerance. Dose-intensive therapy for lung cancer patients is complicated by the fact that this disease most often occurs in an older-aged population (median, 60 to 65 years) with underlying smoking-related comorbid disease, early metastatic spread, and enhanced risk of secondary smoking-related malignancies. In a phase II feasibility trial just activated, patients younger than 60 years of age with limited-stage SCLC are being treated with four cycles of cisplatin and etoposide and concurrent twice-daily chest radiotherapy to 45 Gy (150-6Gy fractions). Those patients achieving complete or near-complete response will receive high-dose cyclophosphamide/cisplatin/carmustine with autologous stem cell support. Upon recovery, prophylactic cranial irradiation will be given. Results could lead to a phase III trial testing the concept of dose intensification. This article reviews evidence for the contribution of dose intensification to response and survival in the treatment of SCLC, the adequacy of the clinical trial's design to address these relationships, and suggestions for future directions. The strategies of dose-intensive induction therapy, multicyle dose-intensive combination therapies, chest radiotherapy, and stem cell purging trials will be discussed.

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In the United States, 180,000 new cases of lung cancer are diagnosed each year, resulting in 163,000 deaths.1 Lung cancer is currently the leading cause of death from cancer in both men and women. Approximately 15 to 25% of all bronchogenic carcinomas, or 30,000 new cases of small cell lung cancer (SCLC), are reported each year in the United States. Dose-intensive therapy for lung cancer patients must allow for an older-aged population (median, 60 to 65 years) with underlying smoking-related cardiovascular and pulmonary disease, as well as enhanced risk of secondary smoking-related malignancies.

The principles of dose response and combination chemotherapy, demonstrated in laboratory models, were basic to the design of initial curative treatment regimens for malignancies that are now curable with chemotherapy.2-6 Combinations of active non-cross-resistant agents are critical to decrease the emergence of drug resistance. Combining agents with different dose-limiting toxic reactions may result in subadditive toxic reactions. Hematopoietic stem cell support, using marrow or peripheral blood progenitor cells, allows evaluation of dose response to the limits of organ tolerance. This article reviews evidence for the contribution of dose intensification to response and survival in the treatment of SCLC, the adequacy of the clinical trial’s design to address these relationships, and suggestions for future directions.

CHEMOTHERAPY

Since SCLC patients usually present with disseminated disease, treatment strategies have focused on systemic therapy. Investigators have observed a high degree of responsiveness to multiple chemotherapeutic agents used both as single agents and in combination regimens. Combination chemotherapy or chemoradiotherapy for limited disease (LD) SCLC (confined to the chest within a single radiation port) produces expected overall and complete response (CR) rates of 80 to 90% and 50%, respectively. While excellent immediate palliation is achieved, long-term progression-free survival remains poor. By 2 years, only 20 to 40% of patients remain alive, of whom half survive 5 years. For extensive disease (ED), expected overall and CR rates are 60 to 80% and 15 to 20%, respectively.7 Fewer than 5% of ED patients survive 2 years.8 Numerous chemotherapeutic agents have major activity against SCLC. The most important of these are etoposide, teniposide, cisplatin, carboplatin, ifosfamide, cyclophosphamide, vincristine, and doxorubicin. Several new agents appear to have at least equivalent activity compared with these established drugs, including the taxanes (paclitaxel and docetaxel), gemcitabine, and the topoisomerase 1 inhibitors (topotecan, irinotecan). Although combination regimens employing established agents have shown activity against SCLC, they produce short- and long-term results that are almost identical to those achieved with single-agent chemotherapy. Over the next few years, we will discover whether the new agents contribute to long-term survival.

Log-linear or near-linear dose-response curves have been obtained for numerous chemotherapeutic agents, particularly the class of alkylating agents, and radiation, but not for antimitabolites, in preclinical in vitro and in vitro experiments.9 The clinical correlation between chemotherapy dose and response for SCLC was originally demonstrated by Cohen et al9 in 1977, using cyclophosphamide, lomustine, and methotrexate, and later confirmed by others.10-14 A few studies9,12 have shown higher

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CR and partial response (PR) rates and a modestly longer median survival time in patients given high-dose chemotherapy, as compared with those given conventional doses of these same agents.

Klaza et al16 performed a meta-analysis using the method of Hryniuk and Bush16 to ascertain whether the dose intensity (expressed in drug dose administered per meter squared per week) of individual agents or regimens correlated with response or survival in SCLC trials. To perform this analysis, it was assumed that all drugs are therapeutically equivalent and that cross-resistance (or synergy) between drugs, peak drug concentrations, or schedule and duration of drug exposure has no effect on treatment outcome. The cyclophosphamide/doxorubicin/ vincristine, cyclophosphamide/doxorubicin/etoposide, and etoposide/cisplatin regimens were evaluated over narrow dose intensity ranges (0.8- to 1.0-fold, 0.6- to 1.7-fold, and 0.75- to 1.8-fold, respectively). Results showed the dose intensities of cyclophosphamide/doxorubicin/vincristine and cyclophosphamide/doxorubicin/etoposide were associated with small prolongations of median survival in SCLC patients.

Most randomized trials evaluating dose intensity have been conducted in ED or mixed-stage SCLC. Arriagada et al17 recently randomized patients with ED SCLC to receive six cycles of either conventional-dose chemotherapy or the same therapy with a modestly dose-intensified first cycle. Results showed the modestly intensified regimen produced improvements in CR and survival over the conventional-dose regimen. It can be argued that randomized trials showing a survival advantage have generally compared less-than-standard with full-dose therapy, whereas trials showing inconclusive results have typically used incremental (between onefold and twofold) increases of conventional-dose chemotherapy.

Dose-limiting toxic reactions have been a problem in studies of dose-intensified chemotherapy. Currently available cytokines (eg, granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor) have helped overcome this problem by shortening chemotherapy-induced myelosuppression and consequent febrile neutropenia.18 Cumulative thrombocytopenia, however, remains dose limiting. Thus, currently, dose and dose intensity can be increased by only 1.5- to 2-fold with cytokine use, differences that are unlikely to produce survival advantages. The effect of various thrombopoietins on achievable dose intensity remains to be seen.

Studies of autologous bone marrow transplantation (ABMT) in SCLC are summarized in Table 1. Patients in these studies were analyzed according to response status (previously untreated, relapsed or refractory, or responding to first-line chemotherapy [PR or CR]) and extent of disease (LD or ED), and pooled for aggregated relapse-free and overall survival characteristics.

Fourteen studies included patients who had either relapsed or refractory disease.19-32 Of 52 evaluable patients, CRs and PRs were observed in 19% and 37%, respectively. However, median duration of these responses was roughly only 2 months, and median survival was approximately 3 months. Combination chemotherapy regimens, especially those containing multiple alkylating agents, appeared to be more effective (overall response rate, 55%; 26% CR rate), but more toxic (18% vs 6% treatment-related mortality) than single-agent therapy. In summary, the observed high overall response and CR rates in these studies support a dose-response relationship in SCLC. High-dose combination chemotherapy, however, did not improve duration of response or survival.

High-dose chemotherapy with ABMT support has been used as initial treatment for 103 patients with SCLC (71% LD),33-40 The overall response and CR rates of 84% and 42%, respectively, and the relapse-free, 2-year, and overall survival rates obtained with high-dose chemotherapy and ABMT support were comparable to treatment with conventional multicyle regimens (7% durable relapse-free survival). Patients with newly diagnosed SCLC frequently have life-threatening complications from uncontrolled disease and therefore may not be optimal candidates for dose-intensified chemotherapy. In addition, untreated autografts have a high rate of tumor cell contamination.

Approximately 292 patients responding to first-line chemotherapy received high-dose chemotherapy with ABMT support.41 Conversion to CR occurred in 50% of partial responders without an overall survival benefit. Dose-intensified chemotherapy shows the most promise in patients with LD in CR at the time of high-dose therapy. Within this subset (excluding the Dana-Farber Cancer Institute/Beth Israel Hospital trial), 35% of patients remained disease free at the time of publication with a median follow-up >3 years.

Much of the experience with high-dose chemotherapy for SCLC occurred during the developmental phase of high-dose therapy for solid tumors. Therefore, many of these high-dose trials employed either single chemotherapeutic agents (with or without low-dose agents) (five series, two with chest radiotherapy,35,36,42-46), single alkylating agents (six series, four with chest radiotherapy,36,38,41,47-50), or combination alkylating agents (eight series, four with chest radiotherapy,51-55). Since high treatment-related morbidity and mortality were encountered in these trials, investigators concluded that the potential benefits of high-dose chemotherapy did not justify the associated risks.

Humblet et al50 treated 101 SCLC patients with chemotherapy for five cycles, and then randomized 45 re-
sponding patients to one cycle of either high-dose (with ABMT) or conventional-dose chemotherapy (Table 2). No chest radiotherapy was given. A clear dose-response relationship was demonstrated with conversion from PR to CR in about 75% of responders receiving high-dose chemotherapy. Among responders receiving conventional-dose chemotherapy, however, no conversions to CR were noted. Disease-free, but not overall, survival was significantly enhanced with high-dose chemotherapy and ABMT. However, the 18% toxic death rate among patients receiving high-dose chemotherapy and ABMT led the investigators to conclude that this treatment approach should not be considered standard for SCLC.

As observed with conventional-dose therapy, patients receiving high-dose, stem cell-supported therapy will generally suffer a relapse in sites of prior tumor involvement.35-49 The high rate of regional relapse may be explained by a greater tumor burden in the chest, host pharmacodynamics reducing drug delivery, and local environmental resistance factors. Since chest relapse occurs in about 90% of individuals following chemotherapy alone vs 60% after radiotherapy, radiotherapy to sites of bulky disease is likely to represent an essential component in curative treatment approaches.

At the Dana-Farber Cancer Institute and Beth Israel Hospital, high-dose combination alkylating agents have been given to >40 patients with LD and >25 with ED SCLC following response to conventional-dose chemotherapy. Of an original cohort of 36 patients with LD (stage IIIA or B) SCLC, 29 were in or near CR prior to treatment with high-dose cyclophosphamide/cisplatin/carmustine with ABMT support followed by chest and prophyactic cranial irradiation.35 With a minimum follow-up of 21 months after completion of high-dose chemotherapy (range, 21 months to 9 years), 52% of patients have remained disease free. Among patients with ED, approximately 20% have remained progression free >2 years after completion of high-dose chemotherapy (A. Elias, MD; unpublished data; August 1996). Local-regional relapse represents about 50% of all relapses.

**FUTURE DIRECTIONS**

**Intensify Involved-Field Radiotherapy**

Numerous randomized trials have demonstrated that the addition of chest radiotherapy provides a 25% improvement in local-regional control and is associated with a 5% increase in long-term progression-free survival for patients with LD SCLC.56-57 However, even with 4,500 to 5,000 cGy of thoracic radiotherapy, the chest relapse rate remains unacceptably high (about a 60% actuarial risk of local relapse by 3 years)58-60 and may be underestimated due to the competing risk of systemic relapse.61 Further enhancement of local-regional control may increase the proportion of long-term survivors, since chest-only relapse is observed in about 40% of patients. If high-dose chemotherapy improves systemic control, initial failure in local-regional sites may become more prevalent.

Few trials have examined the dose intensity of chest radiotherapy. One phase III trial recently administered 45 Gy chest radiotherapy either daily over 5 weeks or twice daily over 3 weeks concurrent with cisplatin/etoposide chemotherapy.62 Intensified chest radiotherapy increased chest control from 39 to 52% actuarial at 2 to 3 years. In a phase I trial, cohorts of five or six patients with LD SCLC were given thoracic radiotherapy either in daily 180-cGy fractions or in twice-daily 150-cGy fractions concurrently with cisplatin/etoposide (N.C. Choi, MD; personal communication: November 1994). The maximal tolerated doses appear to be 45 Gy for twice-daily administration and 66 to 70 Gy when given once daily. Thus, marked dose intensification of radiotherapy appears feasible and should be evaluated in a randomized setting.

The Cancer and Leukemia Group B and Southwest Oncology Group have just activated a phase II feasibility trial stemming from the Dana-Farber Cancer Institute/Beth Israel Hospital experience. Patients younger than 60 years of age with LD SCLC are being treated with four cycles of cisplatin/etoposide with concurrent twice-daily chest radiotherapy to 45 Gy (150-cGy fractions). Those patients achieving CR or near CR will receive high-dose cyclophosphamide/cisplatin/carmustine with autologous stem cell support. Upon recovery, prophylactic cranial irradiation will be given. It is hoped that the results of this trial will lead to a phase III trial testing the concept of dose intensification.

**Intensify Induction Therapy**

Induction therapy reduces tumor burden and facilitates selection of patients with chemoresistant tumors for subsequent dose intensification. Moreover, most SCLC patients present with rapidly progressive systemic and local symptoms. With induction therapy, patient performance status can improve dramatically. However, chemoresistant tumor cells may develop and proliferate. Several strategies might circumvent such resistance. As suggested by Arrigada et al.17 initial intensification of induction therapy may improve disease-free and overall survival. Extension of this concept would be to administer dose-intensive combination chemotherapy with cytokine or peripheral blood progenitor cell support either in repeated cycles of the same regimen43 or in a sequential approach.64-66

**Minimal Residual Tumor/Autograft Involvement**

Since stem cells must be protected from high-dose chemotherapy to make dose escalation feasible, stem cell

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**Table 2—Randomized Trial of Conventional vs High-Dose Chemotherapy in SCLC**

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<thead>
<tr>
<th></th>
<th>High Dose (+ABMT)</th>
<th>Conventional Dose</th>
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<tbody>
<tr>
<td>LD</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>No. of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR to CR, %</td>
<td>77</td>
<td>0</td>
</tr>
<tr>
<td>Disease free at 2 yr, %</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Chest only relapse, %</td>
<td>70</td>
<td>100</td>
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*Adapted from Humblet et al.53 One hundred one patients were given combination chemotherapy plus prophyactic cranial irradiation; 45 patients (32 with LD) were randomized to conventional- or high-dose chemotherapy.
contamination with tumor cells surviving induction therapy may be a source of relapse. While there is extremely persuasive evidence that residual tumor cells contribute to relapse in hematologic malignancies and neuroblastoma, it remains questionable whether currently available purging methods are sufficiently effective to affect survival, or indeed whether the residual tumor in the autograft indicates a residual burden of chemotherapyrresistant tumor cells that is unlikely to be eradicated by high-dose chemotherapy. Gene marking experiments in solid tumors have not yet been informative.

The bone marrow is one of the most common homing sites for metastases. A number of small trials have demonstrated that 13 to 54% of LD and 44 to 77% of ED SCLC cases with normal marrows histologically had subclinical SCLC involvement at diagnosis when examined by immunohistochemical techniques having a sensitivity of detection of one in 104 cells. Fewer data are available for patients undergoing or in response to chemotherapy. Two small series suggest a high rate of residual contamination even after therapy. Hay et al. reported 83% positive screens with no obvious decrement with therapy. A small series from Leonard et al. showed 8 of 12 LD SCLC patients in response had residual tumor cells in the bone marrow detectable by a panel of monoclonal antibodies; 6 of these 8 patients subsequently suffered relapses.

In patients with metastatic SCLC or breast cancer, peripheral blood cells mobilized with granulocyte colony-stimulating factor during the first cycle of etoposide/cisplatin chemotherapy had demonstrable circulating tumor cells. Anecdotally, these investigators have noted lessened or absent tumor cell mobilization after the second cycle of chemotherapy, supporting the contention that in vivo induction chemotherapy can "purge" the patient and the autologous stem cell source.

The observation that numerous chemotherapeutic agents alone and/or in combination possess major activity against SCLC, but with poor long-term clinical outcomes, strongly suggests that these agents are capable of destroying SCLC tumor cells but fail to eradicate a central core of tumor stem cells, which are presumably enriched with various in vivo resistance mechanisms. Identifying these residual cancer cells and systematically evaluating their biological characteristics may guide strategies to specifically target these cells. Minimal residual tumor characterization could then be employed as a determinant for additional treatment, such as modification of chemotherapy, tumor vaccination, or other forms of biological therapy. To this end, the detection of heterogeneity and analysis of patterns of coexpression of various markers form the thrust of our program in the detection of rare cells.

In summary, limited information exists about the incidence of tumor contamination of hematopoietic tissues or the clinical impact of screening in lung cancer patients. With the burgeoning interest and expanding technology in the detection of rare events, prospective trials are needed to evaluate the clinical significance of marrow or peripheral blood tumor contamination, as well as the impact of novel stem cell sources on high-dose chemotherapy.

High-dose chemotherapy can result in prolonged progression-free survival and minimize tumor burden in a select cohort of patients, and may be of greater value in identifying additional targets of residual tumor cells for novel treatment strategies and modalities. Indeed, most biological targets, such as replacement of retinoblastoma and/or p53 gene function or interference with autocrine or paracrine growth loops, and immunologic therapy (interleukin-2, interleukin-12, immunotoxins, tumor vaccine) work best when there is minimal tumor burden.

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