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ORIGINAL ARTICLE

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Dose-intensive therapy in lung cancer

Abstract Lung cancer is epidemic and lethal throughout the world. Overall survival is estimated to be 13% at 5 years despite treatment. The use of chemotherapy in small-cell lung cancer (SCLC) is established, but it is less active against non-SCLC (NSCLC). Since 98% of SCLC cases are associated with heavy smoking and present at a median age of 60–65 years, the application of dose-intensive therapy to lung cancer patients may be complicated by underlying smoking-related comorbidity and an enhanced risk for secondary smoking-related malignancies. The strategies of intensifying induction therapy, multicycle dose-intensive combination therapies, chest radiotherapy, and stem cell purging for both SCLC and NSCLC are discussed herein. Limited data regarding high-dose therapy for NSCLC have been reported. In SCLC, excellent and immediate palliation is achieved through the use of combination chemotherapy. However, by 2 years, only 20–40% of limited-disease- (LD) and $<5\%$ of extensive-disease stage (ED) patients remain alive. Regimens developed using the many established agents produce similar short- and long-term outcomes, an observation that suggests that many of our systemic agents eradicate the same tumor subpopulation but fail to abolish a central core of tumor stem cells, presumably enriched for heterogeneous in vivo resistance mechanisms. The identification of these minimal residual tumor (MRT) cells and systematic evaluation of their biologic characteristics may guide strategies to target these cells specifically; such strategies may include modification of chemotherapy, tumor vaccination, or other forms of biologic therapy, such as replacement of RB, 3p, and/or p53 function; interference with autocrine or paracrine growth loops; or immunologic therapy [interleukin (IL)-2, IL-12, immunotoxins, and tumor vaccines], which would be most effective in the setting of MRT. To this end the detection of heterogeneity and analysis of patterns of coexpression of various markers form the thrust of our MRT detection program. At the Dana-Farber Cancer Institute and Beth Israel Hospital we performed stem-cell autografts in >40 patients with LD SCLC and >25 patients with ED SCLC who were in first response to conventional-dose therapy comprising high-dose combination alkylating agents. Approximately 80% of our patients were in or near complete response after initial chemotherapy. At a minimal follow-up of 23 months (to as long as 10 years) after completion of high-dose chemotherapy in our original trial, 52% of the patients remain disease-free. Of the ED or extrapulmonary patients, approximately 20% remain progression-free at >2 years after high-dose therapy. Local regional recurrence represents about 50% of all relapses. Thus, the roles of thoracic radiation dose intensity and purification of stem-cell autografts are being evaluated in ongoing trials. It is hoped that a cooperative phase III trial testing the concept of dose intensification will begin soon.

Key words Small-cell lung cancer · High-dose chemotherapy · Minimal residual tumor

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Introduction: Rationale for dose-intensive therapy in small-cell lung cancer

Lung cancer is the leading cause of death from cancer in both men and women [8] and is epidemic throughout the world due to increased tobacco consumption. Approximately 15–25% of all bronchogenic carcinomas are small-cell lung cancers (SCLC). The use of chemotherapy in SCLC is established, but it is less active against non-SCLC (NSCLC). Excellent and immediate palliation is achieved through the use of combination chemotherapy; however, by 2 years, only 20–40% of limited-disease- (LD) and $<5\%$ of

extensive-disease-stage (ED) patients remain alive [54, 63]. Overall survival for all lung cancers is estimated to be 13% at 5 years despite treatment.

Numerous chemotherapeutic agents are active against SCLC; the most established of these are cisplatin (and carboplatin), etoposide (and teniposide), ifosfamide, cyclophosphamide, vincristine, and doxorubicin. A number of new agents appear to have activity at least equivalent to that of these established drugs, including taxanes (paclitaxel and taxotere), gemcitabine, and the topoisomerase I inhibitors (topotecan and irinotecan). Combination regimens designed using the established agents produce short-term and almost identical long-term results. Ongoing trials are trying to define the role of the new active agents in first-line therapy.

For the alkylating agents and radiation in particular, but not for antimetabolites, near log-linear dose-response curves in preclinical in vitro and in vivo experiments have been observed [28–31, 72]. The contribution of dose or the dose intensity of chemotherapy to response and survival remains controversial, although in 1977, Cohen et al. [16] demonstrated higher response rates, both complete and partial, and a slightly longer median survival using cyclophosphamide, lomustine, and methotrexate.

Using the methodology of Hryniuk and Bush [36] to ascertain whether the dose intensity (expressed in the drug dose given per square meter of body surface are per week) of individual agents or regimens correlated with response or survival in SCLC trials, Klasa et al. [43] observed that increased dose intensities of cisplatin, doxorubicin, and vincristine or etoposide (CAV or CAE), but not etoposide and cisplatin (EP), were associated with longer median survival in ED patients, but the effects and the dose ranges analyzed were small. This analysis makes the assumption that all drugs are therapeutically equivalent and that cross-resistance (or synergy) between drugs, peak drug concentrations, and the schedule and duration of drug exposure have no effect.

Seven randomized trials have evaluated dose intensity in SCLC, mostly in ED patients [2, 11, 16, 27, 39, 41, 51]. In the only trial treating LD patients exclusively, Arriagada et al. [2] randomized patients to six cycles of conventional-dose chemotherapy with or without a modestly intensified first cycle; intensification resulted in a complete response (CR) and survival advantage. It can be argued that those randomized trials achieving survival advantage generally compared less-than-standard to full-dose therapy, whereas an incremental dose intensity of between one and two full conventional doses did not clearly demonstrate a response or survival advantage.

Current established cytokines [e.g., granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor (G-CSF)] shorten chemotherapy-induced myelosuppression and consequent febrile neutropenia [18], although cumulative thrombocytopenia remains dose-limiting. Thus, at this time, dose intensity can be increased by only 1.5- to 2-fold with cytokine use, differences unlikely to produce survival advantages. The effectiveness of various thrombopoietins in increasing achievable dose intensity remains to be seen. The delivery of dose-intensive therapy to lung cancer patients must take into account a population of greater age (median 60–65 years) with underlying smoking-related cardiovascular and pulmonary comorbidity and an enhanced risk for secondary smoking-related malignancies.

As a review, patients in autologous bone marrow transplantation (ABMT) studies in SCLC were analyzed according to their response status [relapsed or refractory; untreated; responding to first-line chemotherapy [partial response, PR, or CR); and extent of disease (LD or ED)] and then pooled for aggregated relapse-free and overall survival characteristics [23]. In all, 14 studies gave data on 52 patients who had either relapsed or had refractory disease [21, 22, 25, 34, 46, 56–58, 60, 61, 66, 67, 69, 78]. CRs and PRs were observed in 19% and 37% of cases, respectively. However, the median response duration was approximately 2 months and the median survival approximately 3 months. Combination chemotherapy regimens, particularly those containing multiple alkylating agents, appeared to be more effective (response rate 58%, CR 26%) but more toxic (18% versus 6% deaths) with no effect on the duration of response or survival. The observed high overall response and CR rates support a dose-response relationship, but it is not sufficent to improve survival.

As initial treatment, high-dose therapy produced overall response and CR rates of 84% and 42%, respectively, in 103 SCLC patients (71% of whom had LD) [25, 40, 45, 48, 49, 52, 65, 68]. Relapse-free 2-year and overall survival rates were comparable to those obtained using treatment with conventional multicycle regimens. ABMT in newly diagnosed SCLC may not be optimal due to the frequency of life-threatening complications from uncontrolled disease and to the potential for tumor-cell contamination in untreated autografts.

Approximately 282 patients responding to first-line chemotherapy received high-dose chemotherapy with autologous marrow support as intensification [26]. Of the patients achieving only a PR in response to induction therapy, conversion to CR occurred in 50%, but without durable effect. The best results (35% progression-free at a median follow-up of >3 years at the time of publication) were reported in LD patients in CR at the time of high-dose therapy.

Many of the high-dose SCLC studies reviewed were conducted during the initial 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 in addition; five series, two with chest radiotherapy) [4, 5, 14, 45, 50, 64, 65], single alkylating agents (six series, four with chest radiotherapy) [20, 26, 38, 44, 45, 66, 68], or combination alkylating agents (eight series, four with chest radiotherapy) [17, 24, 37, 52, 58, 69, 71, 77]. Higher treatment-related morbidity and mortality than are currently expected were observed in these studies.

Humblet et al. [37] treated 101 SCLC patients with chemotherapy for 5 cycles, of whom 45 were eligible for randomization to one further cycle of either high-dose or conventional-dose therapy with cyclophosphamide, etopo-

side, and carmustine; no chest radiotherapy was given. A dose-response relationship was demonstrated. Conversion from a PR to a CR occurred in about 75% of patients after high-dose therapy as compared to none after conventional-dose treatment. Disease-free survival was significantly enhanced, and a trend toward improved survival was observed. However, an 18% toxic death rate on the ABMT arm led the investigators to conclude that dose-intensive therapy should not be considered a standard therapy in SCLC. Moreover, since chest radiotherapy was not given in this trial, disease in almost all the patients who relapsed recurred in the chest.

Patients generally relapse at sites of prior tumor involvement [62, 65]. The high rate of locoregional relapse may be explained by the greater tumor burden in the chest, the possible presence of drug-resistant clones or NSCLC elements, poorer drug delivery, or intratumoral resistance factors such as hypoxia. Since chest relapse occurs in about 90% of individuals following chemotherapy alone and in 60% after radiotherapy, radiotherapy to sites of bulky disease is likely to represent an essential component of curative treatment approaches.

At the Dana-Farber Cancer Institute (DFCI) and Beth Israel Hospital (BIH), >45 patients with LD SCLC and >25 patients with ED SCLC were treated with high-dose combination alkylating agents following a response to conventional-dose induction therapy. Of the original cohort of 36 LD SCLC patients (all had N2 or N3 disease), 29 were in or near CR prior to treatment with high-dose cyclophosphamide, carmustine, and cisplatin with bone marrow (plus peripheral blood stem-cell in some cases) support followed by chest and prophylactic cranial radiotherapy [55]. At a minimal follow-up of 23 months after the completion of high-dose chemotherapy (range 23 months to 10 years), 52% of our patients remain disease-free. Of the ED patients, 18–20% remain progression-free at >2 years after high-dose therapy (Elias, unpublished results). Locoregional relapse represents about 50% of all relapses.

Future directions

Intensifying involved-field radiotherapy

As summarized in meta-analyses, randomized trials have demonstrated that chest radiotherapy provides a 25% improvement in locoregional control and a 5% increase in long-term progression-free survival for LD SCLC [59, 76]. However, even with 45- to 50-Gy thoracic radiotherapy, chest relapse remains unacceptably high (about a 60% actuarial risk for local relapse by 3 years) [13, 42, 55] and may be underestimated due to the competing risk of systemic relapse [1]. Since chest-only relapse is observed in about 40% of patients, further enhancement of locoregional control may increase the proportion of long-term survivors. If systemic control is improved by high-dose chemotherapy, initial failure in locoregional sites may become more prevalent.

The dose intensity of chest radiotherapy has not been well studied. The Eastern Cooperative Oncology Group/Radiotherapy Oncology Group recently reported a comparison of 45-Gy chest radiotherapy given either daily over 5 weeks or twice daily over 3 weeks concurrent with cisplatin and etoposide chemotherapy [75]. Intensified chest radiotherapy reduced chest failure from 61% to 48% actuarial risk at 2–3 years ($P<0.05$). Dr. N.C. Choi et al. (personal communication) have escalated the dose of radiotherapy in cohorts of five to six patients with LD SCLC. Thoracic radiotherapy was given concurrently with cisplatin and etoposide either as daily 180-cGy fractions or as twice-daily 150-cGy fractions. The maximal tolerated doses appear to be 45 Gy for twice-daily administration and 66–70 Gy for therapy given once daily. Thus, marked intensification of the radiotherapy dose appears to be possible 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 DFCI/BIH experience. Patients aged <60 years with LD will be treated with four cycles of cisplatin and etoposide with concurrent twice-daily chest radiotherapy to 45 Gy (150-cGy fractions). The patients achieving a CR or near-CR will receive high-dose cyclophosphamide, cisplatin, and carmustine with autologous stem-cell support. Upon recovery, prophylactic cranial irradiation will be given. It is hoped that this will lead to a phase III trial testing the concept of dose during intensification.

Intensifying induction

Induction therapy reduces the tumor burden and allows the selection of patients with chemosensitive tumors for subsequent intensification. Moreover, it can control rapidly progressive systemic and local SCLC symptoms and improve the performance status dramatically. In contrast, during induction, chemoresistant tumor cells may develop and proliferate and have even been induced by induction therapy. Several strategies might circumvent such resistance. As suggested by the trial conducted by Arriagada et al. [2], initial intensification of induction may improve disease-free and overall survival. A logical extension of this concept would be to carry out multicycle dose-intensive combination therapies supported by cytokines and peripheral blood progenitor cells using either repeated cycles of the same regimen [73] or a sequence of different agents [3, 19, 32].

Minimal residual tumor/autograft involvement

Since stem cells must be protected from high-dose therapy to make dose escalation feasible, stem-cell contamination with tumor cells that have survived induction therapy may be a source of relapse. Residual tumor cells contribute to relapse in certain hematologic malignancies and neuroblastoma ([9, 10, 33]; Dr. M.K. Brenner, personal communication). It is not clear whether currently available purging

methods are sufficiently effective or whether the residual tumor in the autograft indicates that the patient is burdened by chemotherapy-resistant tumor cells uneradicable by high-dose therapy. Gene-marking experiments in solid tumors have not yet provided definitive information [53].

Bone marrow is one of the most common homing sites for metastases. Small trials have demonstrated that 13–54% of LD SCLC patients and 44–77% of ED SCLC patients with histologically negative bone marrow had subclinical SCLC bone marrow involvement at diagnosis when examined by immunohistochemistry techniques, which have a sensitivity of detection of 1 in 10^4 cells [6, 7, 15, 70, 74]. Two small series suggest a high rate of residual contamination even after successful therapy: Hay et al. [35] reported an 83% rate of positive screens with no obvious decrement with therapy, and Leonard et al. [47] found that 8 of 12 LD SCLC patients in response had residual tumor cells in their bone marrow as detected using a panel of monoclonal antibodies, of whom 6 subsequently relapsed. In patients with metastatic SCLC or breast cancer, peripheral blood cells mobilized using G-CSF during the first cycle of etoposide, ifosfamide, and cisplatin (VIP) chemotherapy had demonstrable circulating tumor cells, although their viability was not evaluated [12]. Mobilization of tumor cells after the second cycle of chemotherapy was not observed, supporting the contention that in vivo chemotherapy induction can purge the patient and the autologous stem-cell source.

Conclusions

The disparity between the high clinical activity of numerous chemotherapeutic agents against overt SCLC and the uniformly poor clinical outcome suggests that many of our systemic drugs fail to eradicate a central core of tumor stem cells that are presumably enriched for in vivo resistance mechanisms. Identification and characterization of these residual cancer cells may guide therapeutic strategies to target these cells specifically. Minimal residual tumor characterization could then be employed to determine additional treatment. Thus, the detection of heterogeneity and analysis of patterns of coexpression of various markers are the focus of our effort to detect rare cells. Prospective trials to evaluate the clinical significance of marrow or peripheral blood tumor contamination and the ability of novel stem-cell sources to support high-dose therapy are needed.

High-dose therapy can result in prolonged progression-free survival. In an additional group of patients it may result in a minimal residual tumor burden (near-cure). To the extent that additional targets of residual tumor cells can be identified for novel treatment strategies and modalities, high-dose therapy may be of great value. Most biologic strategies, such as replacement of the retinoblastoma gene and/or p53 function, interference with autocrine or paracrine growth loops, and immunologic therapy [interleukin (IL)-2, IL-12, immunotoxins, and tumor vaccines], work best against a minimal tumor burden.

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