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REVIEW

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Importance of dose and dose intensity in the treatment of small-cell lung cancer

Abstract This review examines the rationale and outcomes of intensive chemotherapy trials for small-cell lung cancer (SCLC) to determine whether further clinical research in this area is likely to generate improved results. Animal model experiments for intensive chemotherapy were reviewed to determine whether results observed in the laboratory predicted the outcomes seen in clinical trials. In addition, phase III randomized trials that differ only by the quantity of chemotherapy drug delivered were examined, with particular attention being paid to whether the conclusions reached were consistent when limited-stage and extensive-stage SCLC were separately studied. The most clear-cut evidence of benefit in animal model experiments comes from models with curative potential. In clinical trials, when dose and dose intensity are diminished from standard levels the effect is detrimental for both limited- and extensive-stage SCLC. Trials of dose and dose intensity above standard levels have not yet shown advantages for patients with extensive-stage SCLC. However, the only two randomized trials of chemotherapy dose escalation for limited-stage SCLC show statistically significant survival benefits. Therefore, animal model experiments have accurately predicted conclusions reached in SCLC clinical trials. Future studies of intensive chemotherapy for SCLC should focus on the limited-stage group.

Key words Small-cell lung cancer · Chemotherapy · Dose intensity

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Introduction

Chemotherapeutic strategies in the clinic have developed by a largely empirical tradition. Irrespective of the final objective, most oncologists favor giving drugs at near the maximum tolerated dose (MTD) at a frequency determined by recovery from acute toxicity such as granulocytopenia. However, the three main chemotherapeutic objectives of cure, symptom relief, and survival gain may require different strategies to optimize the therapeutic ratio for each. Much effort has been made to develop an improved strategy for curative chemotherapy. The avoidance of a drug-refractory clone has been accepted as a fundamental requirement for curative systemic therapy, and a mathematical model [8] of the development of drug resistance is widely accepted. In the curative setting, the chemotherapy protocol must deliver an adequate dose, dose intensity, and total dose to eliminate all disease. Strategies suggested by the Goldie-Coldman model may not be appropriate for patients who have metastatic spread of a drug-refractory clone. In the noncurative setting, treatment intensity must be sufficient to control chemosensitive elements until resistant tumor becomes dominant.

The major treatment variables in a chemotherapy protocol are described in Table 1. From this information the parameters of drug delivery can be calculated [4], including the single dose size (in milligrams per square meter of body surface area), the dose rate or dose intensity (in milligrams per square meter per week), and the total dose (in milligrams per square meter). Although many clinical trials of treatment of small-cell lung cancer (SCLC) have been performed, it is disappointing that the optimal drug-delivery parameters are not free of controversy for any regimen. Moreover, it has not been determined whether these parameters differ when treatment is given with curative as opposed to palliative intent.

The interdependence of dose, dose intensity, and total dose is shown in Fig. 1. An experimental protocol designed to determine a particular treatment parameter should ideally vary only that factor while keeping the other two aspects of

Table 1 Treatment protocol variables and drug-delivery parameters

Treatment protocol variables:
1. Drug selection and diversity
2. Dose (BSA or weight)
3. Route
4. Interval
5. Dose modification for toxicity
6. Number of cycles or duration (total dose)
Parameters of drug delivery:
1. Dose (mg/m^2)
2. Dose intensity (mg/m^2 per week)
3. Total dose (mg/m^2)

drug-delivery constant. For example, if one were attempting to assess dose intensity, the total dose and single dose size should be held constant and the dose intensity should be altered by changing the interval between treatments. Similarly, if single dose size were the experimental variable, treatment frequency should change such that the dose intensity remain constant and the total dose is kept identical. Drug-delivery studies are hardly ever performed in this fashion because usually the dose, dose intensity, and total dose are modified simultaneously by changing single dose size while keeping the same dosing interval and number of cycles. The extent to which these design flaws in chemotherapy delivery trials have undermined our acquisition of knowledge in this field is difficult to determine.

Influence of stage on the impact of drug-delivery innovations

After examining a large body of data from experimental animal models, Schabel et al. [16] concluded that "The dependence upon maximal dosing for greatest tumor cell kill and optimal therapeutic effect is probably the most consistent principle in cancer chemotherapy that we observe with essentially all drugs in murine tumor models, and we believe clinical protocol planning would be well guided by using it." The examples cited to support this quotation include animal tumor models with curative potential [17]. When Skipper [18] retrospectively analyzed large bodies of these data on the independent (or semi-independent) effects of dose intensity and total dose, he developed the following generalization: "Dose intensity is the dominant treatment design variable with respect to the degree of therapeutic response (cure or nearness to cure at the nadir); total dose, however, often correlates best with the duration of response of treatment failures (i.e., the duration of temporary partial remissions and complete remissions and survival time of treatment failures). High dose intensity for a relatively short duration is the best choice when cure is the goal (and feasible), but lower dose intensity for longer periods may be the best choice when palliation is the goal."

Although the limited-stage (LSCLC) versus extensive-stage (ESCLC) SCLC Veteran's Administration system evolved to facilitate decisions about thoracic irradiation delivery, it is clear that the stage distinction has biologic implications beyond the occurrence of metastatic events.

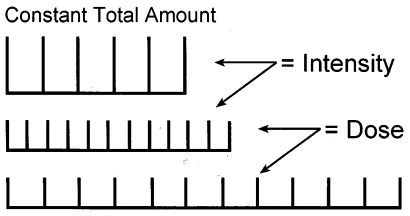

Fig. 1 Interdependence of dose, dose intensity, and total dose

Due to the prevalence of drug-resistant clones, LSCLC and ESCLC are qualitatively and quantitatively different. LSCLC is a model of a curable malignancy; ESCLC is a model of an incurable malignancy. This review examines separately the effects of innovations in chemotherapy delivery on the outcome of ESCLC and LSCLC. The conclusions are often different.

Standard regimens

Commonly used combination chemotherapy regimens for SCLC are usually assembled from five drugs or their analogues. Many permutations and variations of regimens containing cyclophosphamide (C), doxorubicin (A), vincristine (V), etoposide (E), and cisplatin (P) have been reported, and a number of regimens have been used in many phase III studies. The standard cycle interval is 3 weeks. CAV, CAVE, EP, and alternating CAV/EP combinations have been used most consistently by Japanese and North American cooperative groups.

Dose and dose-intensity escalation in ESCLC

A meta-analysis of outcome in LSCLC and ESCLC treated with dose and dose-intensity variations of CAV, EP, and CAVE showed no consistent evidence for better response rates or median survival (long-term survival was not examined) for more intense regimens [12]. However, the range of dose intensities was narrow because most regimens used standard dose intensities as determined in previous phase I–II pilot studies. A standard dose is defined as 75–90% of the MTD.

Only one randomized trial has compared standard-dose treatment to half-standard-dose therapy. This study, conducted by Cohen et al. [2], required only 32 patients to demonstrate the detrimental effect of reducing standard doses of lomustine (100 mg/m^2) and cyclophosphamide (1000 mg/m^2) by 50% in a 3-drug regimen including methotrexate. It is unfortunate that more trials of this design (with larger numbers of patients) examining modern regimens do not exist, as exploration of the steep portion of the dose and dose-intensity-response curves yields fundamental knowledge of drug action. The detrimental effect of low dose intensity could theoretically be offset in the palliative setting by a larger total dose [3]. However, such an experiment is unlikely to be successful in practice because poor control of a virulent tumor such as SCLC would

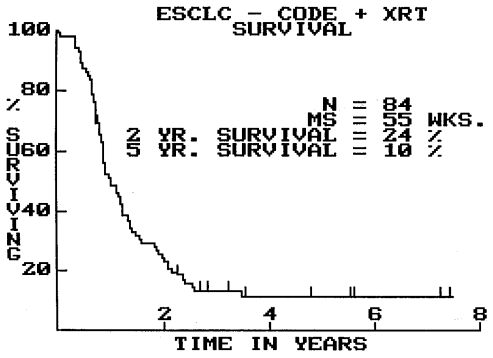

Fig. 2 Crude survival of ESCLC patients (*n*=84) in the Vancouver pilot study of CODE chemotherapy plus radiotherapy. Median survival 55 weeks; 2-year survival 24%; 5-year survival 10%

preclude long-duration treatment. Standard dose intensity cannot be halved without decreasing efficacy in LSCLC or ESCLC.

The SCLC trials designed to assess the value of dose intensity greater than standard have most frequently been performed in the incurable ESCLC group. An early study [9] examined the addition of high and low doses of methotrexate to CAV in a population of ESCLC patients. No survival difference was observed. When higher doses of CAV [6, 11] or EP [10] were compared to standard doses in phase III ESCLC trials, toxicity was worse and outcomes were no better. The plateau of the dose-response or the intensity-response curve in the palliative setting and the MTD appear to be similar; the biologic basis of this relationship has not been clearly explained. It is probable that both standard and intensely applied chemotherapy are capable of eliminating most of the chemosensitive tumor, but when the resistant clone becomes dominant, this invulnerable portion of the cancer determines the prognosis.

Another method of increasing the intensity of a regimen is to add more drugs at full intensity rather than to increase the intensity of the few drugs within the combination. This was the rationale for the development of the cisplatin, vincristine, doxorubicin, and etoposide (CODE) regimen at the University of British Columbia [15]. This weekly protocol alternates myelosuppressive and nonmyelosuppressive therapy weeks, with steroids and prophylactic antibiotics being given as supportive care. CODE intends to deliver as much cisplatin, more doxorubicin, more vincristine, and more etoposide in 9 weeks than does the alternating CAV/EP regimen in 18 weeks; CODE includes no cyclophosphamide. In the Vancouver pilot study, patients responding to CODE without residual disease outside the chest after chemotherapy received consolidative thoracic irradiation and prophylactic cranial irradiation. The population treated was a select group with a good performance status; patients aged >65 years were excluded. A recent update of the data shows a complete response (CR) rate of 48% (thoracic response was assigned by chest radiograph rather than by computed tomography scan), a median survival of 55 weeks, 2-year survival of 24%, and 5-year survival of 10% (Fig. 2). This study generated hopes that the cure barrier could be broken in ESCLC, resulting in a small but definite proportion of long-term survivors.

Two phase III trials comparing the CODE regimen to standard alternating CAV/EP have been completed. The study by the Japanese Clinical Oncology Group (JCOG) and the intergroup National Cancer Institute of Canada and Southwest Oncology Group (NCIC/SWOG) trial differed in a number of respects. Differences included the age eligibility (patients aged >65 years were allowed by the JCOG but not by the NCIC/SWOG), the etoposide administration route (all etoposide was given intravenously in the JCOG study and orally on days 2 and 3 in the NCIC/SWOG trial), the cyclophosphamide dose (20% lower in the JCOG trial than in the NCIC/SWOG trial), and the radiotherapy policy (thoracic and cranial radiotherapy was given to responders in the NCIC/SWOG trial but was not used routinely in the JCOG study). An important additional difference between the trials was the type of supportive care given: the JCOG used granulocyte colony-stimulating factor (G-CSF), whereas the NCIC/SWOG used steroids (prednisone) and prophylactic antibiotics (co-trimoxazole).

The JCOG study was presented at the 1996 American Society of Clinical Oncology meeting by Furuse et al. [7]. It is noteworthy that the median age of 64 years in the JCOG trial is higher than the usual median age in North American SCLC trials (61 years) and higher still than that in the NCIC/SWOG CODE trial (58 years). G-CSF as used by JCOG appeared to allow delivery of the CODE protocol with good fidelity; about 85% of patients received all 9 weeks of intended treatment within 10 weeks. Although the overall response rate was somewhat higher for patients receiving CODE (85.3%) than for those given CAV/EP (76.7%), the difference was not statistically significant and the proportion of CRs was about 15% in both arms. The survival curves separate in favor of CODE, but the median survival (11.9 months for CODE and 10.6 months for CAV/EP) differs by only 6 weeks and the probability value is not significant.

On the basis of the Vancouver pilot study [15], treatment-related mortality in the NCIC/SWOG trial was anticipated to be 3–4%. Unfortunately, after 220 patients had been accrued the toxic death rate on the CODE arm reached 9%. The steroids and antibiotics were insufficient to protect patients from CODE toxicity in the multi-institutional setting. On the basis of toxicity and an interim analysis the trial was closed in April 1996. Drug-delivery and response-rate analyses are not available at this time. The median survival in both arms is about 1 year, and approximately 20% of patients are alive at 2 years.

Taken together, the preliminary results of the phase III comparison of CODE and CAV/EP by JCOG and NCIC/SWOG do not support the superiority of intense multiagent chemotherapy for ESCLC. Although the median survival outcomes observed for CODE in both phase III trials are similar to that seen in the Vancouver pilot study (about 1 year), the patient populations overall appear to have better prognostic factors than those in many ESCLC trials. Mature results of the JCOG and NCIC/SWOG studies will be of

Table 2 Phase III LSCLC trials using etoposide/cisplatin chemotherapy (*NCCTG* North Central Cancer Treatment Group, *CALGB* Cancer and Leukemia Group B, *ELCWP* European Lung Cancer Working Party)

Group	Question
SWOG	Supportive care/maintenance: granulocyte-macrophage colony-stimulating factor and interferon
JCOG	Radiotherapy timing: early vs late
Intergroup	Radiotherapy: standard vs accelerated
NCCTG	Radiotherapy: standard vs hyperfractionated
CALGB	Resistance modification: tamoxifen vs control
Australia	Supportive care: carboplatin/etoposide ± G-CSF
ELCWP	Cisplatin fractionation

interest with respect to the proportion of long-term survivors.

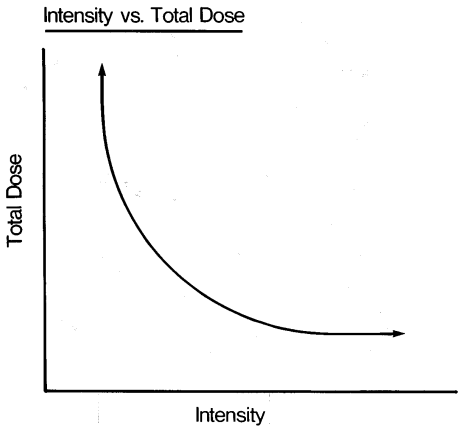

Fig. 3 Theoretical mathematical relationship between total dose and dose intensity. The *rectangular hyperbole* shows the amount of chemotherapy required to control a given quantity of chemosensitive tumor

Dose and dose-intensity escalation in LSCLC

Only 2 randomized trials [1, 13] of chemotherapy intensity in LSCLC involving more than 50 patients per arm have been reported. Both demonstrated significant survival benefits in this potentially curable population. The Eastern Cooperative Oncology Group [13] randomized 349 patients with SCLC (38% of whom had LSCLC) to induction chemotherapy with 1500 mg/m^2 cyclophosphamide given on days 1 and 22, 70 mg/m^2 lomustine given on day 1, and 15 mg/m^2 methotrexate given twice per week on weeks 1, 2, 5, and 6 (without dose modification for hematologic toxicity) or to treatment with the same drugs but with 700 mg/m^2 cyclophosphamide (with dose modification for hematologic toxicity). This important study has been published in abstract form only and thoracic irradiation is not mentioned. For LSCLC patients the median survival was 56 weeks for high-dose therapy and 42 weeks for standard therapy (P=0.02). Survival among ESCLC patients did not differ significantly. Long-term outcomes were not reported.

After retrospective review of treatment data on alternating chemotherapy and radiotherapy regimens for LSCLC, investigators at the Institut Gustav-Roussy [1] concluded that the impact of the size of the initial dose of cyclophosphamide and cisplatin should be assessed in a controlled trial. Patients were randomly assigned to receive different doses of cisplatin and cyclophosphamide as follows: 100 mg/m^2 on day 2 and 300 mg/m^2 on days 2–5 versus 80 mg/m^2 on day 2 and 225 mg/m^2 on days 2–5. The doses of doxorubicin (40 mg/m^2 given on day 1) and etoposide (75 mg/m^2 given on days 1–3) remained the same. The increased doses of cisplatin and cyclophosphamide were given for one cycle only; subsequently, all patients received the same schedule of alternating chemotherapy and radiotherapy with the lower doses of cisplatin and cyclophosphamide. The complete remission rate recorded for the 55 patients in the high-dose group (67%) was not significantly better than that noted for the 50 patients receiving the lower initial dose (54%). However, a significant difference in overall survival (P=0.01) was observed in favor of the patients who received the single escalated drug dose.

The data available from phase III trials of dose intensity of chemotherapy for LSCLC do not allow a confident statement to be made about the optimal dosing schedule. The point to be stressed is that the lack of efficacy of dose and dose-intensity escalation in the palliative setting of ESCLC does not mean that such strategies are not worthwhile for curative therapy of LSCLC. More investigation in this area is needed.

Sequential use of etoposide and cisplatin has become popular as the chemotherapy of choice for LSCLC worldwide as evidenced by the recent phase III trials listed in Table 2. The other major factor that has driven the popularity of the use of EP in LSCLC is the manageable toxicity associated with the administration of this regimen with concurrent thoracic irradiation. From the earliest report [14] it was evident that concurrent EP and thoracic irradiation had less pulmonary, cutaneous, and esophageal toxicity than other chemotherapy regimens and importantly, both modalities could be given without compromising the dose or timing. However, it is curious that the EP regimen should be accepted as standard chemotherapy for curable LSCLC when it has never demonstrated a significantly superior survival benefit over any other combination of drugs in any phase III trial in LSCLC or ESCLC. Nevertheless, the international popularity of EP for LSCLC as described in Table 2 speaks for itself, although, interestingly, none of the studies listed addresses the crucial issue of dose or dose intensity. The questions studied include supportive care, interferon maintenance, resistance modification, cisplatin fractionation, radiotherapy timing, and radiotherapy fractionation.

Although a randomized comparison of EP dose intensity has not shown benefit for palliative therapy of ESCLC [10], such a trial in LSCLC would be of considerable scientific interest. Both arms should have the same dose of EP, but by a decrease from 3 weeks to 2 weeks in the interval between cycles in one arm an increase in dose intensity of 50% could be achieved. Hematologic supportive care with cyto-

kines would probably be required for the more dose-intense schedule, and such therapy would have to be compatible with early thoracic irradiation integrated with EP chemotherapy. Such investigations would provide badly needed information on the importance of dose intensity in LSCLC.

High-dose chemotherapy

An extension of the dose-response relationship is the delivery of very-high-dose chemotherapy supported by autologous bone marrow or peripheral progenitor cell support. Although results have not been encouraging in relapsed SCLC or ESCLC, consolidation of LSCLC after induction chemoradiation is more appealing conceptually. The promise of such therapy is not only eradication of residual chemosensitive tumor but also elimination of elements that are refractory to standard dosing. This line of research has been discussed in detail by Elias [5].

Relationship between dose intensity and total dose

During the retrospective analysis of hundreds of multi-armed trials in animal model systems performed at the Southern Research Institute [18], plots of dose intensity against total dose were developed where the end point was the dose at which 10% of the animals died due to toxicity (LD_{10}). Fatal toxicity in mice may be viewed as a surrogate for elimination of chemosensitive tumor. The U-shaped curves generated are similar to the theoretical curve shown in Fig. 3 and predicted by mathematical models of drug-delivery [3]. The curve describes the amount of treatment required to control a given quantity of chemosensitive tumor; the elimination of all chemosensitive tumor defines the useful duration of chemotherapy.

The curve is mathematically described as a rectangular hyperbole. At one asymptote is the quantity of chemotherapy required to control precisely the amount of tumor that regrows between treatments. The other asymptote represents a single high-dose treatment that destroys all chemosensitive tumor in one application. The greater the dose intensity of the chemotherapy given, the smaller the total dose required.

Data from SCLC clinical trials have not proven the existence of the curve. Such a dramatic relationship may not be obvious clinically because the point of elimination of all chemosensitive tumor is an undetectable end point in patient care. Moreover, the notorious behavior of tumor clones refractory to chemotherapy dominates the clinical picture in this disease. The practical importance of this hypothesis is that if future studies do demonstrate better outcomes with intensive regimens, particularly in the curable LSCLC group, protracted exposure to toxic chemotherapy according to existing guidelines of treatment duration (3 or 4 months) may not be necessary.

Conclusions

Data from experimental animal tumor models indicate that increases in dose and dose intensity would enhance the cure rate mainly in systems where conventional dosing has been capable of generating a consistent proportion of cures. In SCLC the group of patients most studied with intensive therapy has been the incurable ESCLC group, and results show no significant improvement in terms of survival. Trials performed to date on curable LSCLC patients have provided more hope, and future investigations should focus on this group.

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