Cancer Chemother Pharmacol (1997) 40 (Suppl): S107–S109

ORIGINAL ARTICLE

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Chemotherapy for small-cell lung cancer: more is not better

Abstract As have many other chemosensitive tumors, small-cell lung cancer (SCLC) has a well-documented chemotherapy dose-response relationship. However, a relationship between dose and survival has not yet been established. The effect of dose on survival should be examined in terms of both the dose used over a certain period (dose intensity) and the total dose of drugs employed, and neither the total dose of drugs used nor the duration of maintenance chemotherapy has been proven to provide an overall survival benefit. In the case of the dose-intensive approach there is no evidence for a significant survival benefit of either high-dose or dose-intensive weekly chemotherapy. Stem-cell support may be a promising means of increasing dose intensity, but the indications are limited and it should be considered highly experimental. Given the relatively good condition of patients in most comparative clinical trials, more is not better in chemotherapy for SCLC, at least in clinical practice.

Key words Small-cell lung cancer · Maintenance chemotherapy · Dose intensity · Stem-cell support

Work presented at the 12th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium, "New therapeutic strategies for higher cure rates: High-dose therapy and new therapeutic modalities," 4–5 October 1996, Nagoya, Japan

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Introduction

Small-cell lung cancer (SCLC) accounts for approximately 20% of all lung cancers and is characterized by its high rate of response to chemotherapy [12]. Combination chemotherapy for SCLC provides a survival benefit, but 2-year survivors are rare, particularly among patients with extensive disease [11]. As for many other chemosensitive tumors, the dose-response relationship of SCLC is well documented [14]; however, a dose-survival effect has not yet been established. In considerations of the effect of dose on survival the total dose of drugs employed as well as the dose used over a period (dose intensity) must be taken into account.

Maintenance chemotherapy

To determine the effect of the total dose of drugs on survival, many investigators have attempted to give more drugs as maintenance chemotherapy, although most randomized trials have failed to demonstrate survival prolongation. According to our Medline search, of 11 randomized controlled trials comparing induction with induction plus maintenance chemotherapy, many recent studies failed to demonstrate any effect of maintenance on survival [2–5, 7, 10, 17–21] (Table 1).

In 1993, Giaccone et al. [10] reported that 5 cycles of cyclophosphamide, doxorubicin, and etoposide (CDE) produced the same outcome as 12 cycles of therapy, with the survival curves being almost identical. From this study we concluded that even recently developed drug combinations used for >1 year are no more effective than 6-month regimens.

High- versus standard-dose chemotherapy

In recent years, two phase III trials comparing high- and standard-dose therapy for extensive-stage SCLC have been conducted [13, 15]; neither study demonstrated survival

Table 1 Phase II trials of maintenance chemotherapy in SCLC (*CMV* Cyclophosphamide, methotrexate, vincristine, *VAC* vincristine, doxorubicin, cyclophosphamide, *CAV* cyclophosphamide, doxorubicin, vincristine, *PE/CVM* cisplatinum, etoposide/cyclophosphamide, vincristine, methotrexate, *CVME* cyclophosphamide, vincristine, methotrexate, etoposide, *CEV* cyclophosphamide, etoposide, vincristine, *CAV-HEM* cyclophosphamide, doxorubicin, vincristine/hexamethylmelamine, etoposide, methotrexate, *CCNU-CAE* lomustine, cyclophosphamide, doxorubicin, etoposide, *CDE* cyclophosphamide, doxorubicin, etoposide, *IEA* ifosfamide, etoposide, an anthracycline (doxorubicin or epirubicin). *LD* limited-disease, *CR* complete response, *ED* extensive disease, *PR* partial response, *NC* no change, *NS* not significant)

Regimen (induction→maintenance)	Eligibility for maintenance trial	*n*	Survival (months)		*P* (difference between survival curves)	Reference
			Maintenance	No maintenance		
CMV×6→CMV until relapse	LD-CR	46	16.8	6.8	0.01	[18]
VAC×6→×8	ED-CR, PR	61	12.4	8.6	0.006	[4]
CMV×6→PE×2	LD-CR, PR	148	22.8	15.9	0.0094	[5]
PE/CVM×3→CVM×6	LD-CR, PR, NC	66	14.1	19.2	0.05	[3]
CVME×6→×6	LD-CR, PR	265	8.2	7.8	NS	[19]
CEV×4→×4	LD+ED	610	9.1	7.5	NS	[21]
CAV×6→8	ED-CR	86	9.6	6.9	NS	[7]
CAV-HEM×3–4→×3	ED-CR		11.4	14.2	NS	[7]
CCNU-CAE×6→×6	LD+ED-CR	79	11		NS	[17]
CVME×3→×3	LD+ED	309	7.4	8.6	NS	[2]
CDE×5→×7	LD+ED-CR, PR, NC	415	9.3	9.3	NS	[10]
IEA×6→EV×12	LD+ED-CR, PR	91	11.2	8.9	NS	[20]

benefits for high-dose therapy. Ihde et al. [13] compared high-dose cisplatin and etoposide (PE) with a standard-dose regimen. One group of patients received two cycles of high-dose therapy followed by two cycles of standard-dose therapy; a second group received four cycles of standard-dose therapy. The relative dose intensity was 46% greater in the high-dose group. The complete response rate and median survival duration were identical in these two groups, whereas the incidence of toxicity was significantly greater in the high-dose group.

Johnson et al. [15] compared three cycles of high-dose cyclophosphamide, doxorubicin, and vincristine (CAV) followed by three conventional-dose cycles with six cycles of conventional-dose therapy. The survival curves generated for the two groups were identical, and life-threatening leukopenia and infections were more common in the high-dose arm. Furthermore, in a meta-analysis designed to determine the possible relationship between the intended dose intensity and the response or median survival in 60 trial reports, Klasa et al. [16] found no significant correlation between the cyclophosphamide or doxorubicin dose intensity and the median survival of patients.

Arriagada et al. [1] compared high doses of cyclophosphamide and cisplatin combined with standard doses of doxorubicin and etoposide with standard doses of these drugs, with high-dose therapy being used only during the first cycle of chemotherapy. The higher dose resulted in better disease-free and overall survival, but high-dose cisplatin and cyclophosphamide were only 20% and 25%, higher, respectively, than the standard doses used in this study. The total dose and dose intensity over the six cycles of treatment were similar; therefore, Arriagada et al. [1] stressed the importance of using high drug doses in the initial cycle. However, it should be noted that only limited-stage SCLC patients were enrolled in this study and that the protocol included thoracic irradiation. These factors may have influenced the outcome, and confirmation of these results awaits further trials.

In 1992, Fukuoka et al. [8] showed that a dose-intensive cisplatin, vincristine, doxorubicin, and etoposide (CODE) regimen with granulocyte colony-stimulating factor (G-CSF) support produced better response and survival rates than did the same regimen without G-CSF support. The Japan Clinical Oncology Group (JCOG) went on to compare CODE with G-CSF support with the standard alternating CAV/PE regimen. Furuse et al. [9] reported that the response rates were the same in the two arms of this trial and that the median survival was 11.5 months in the CODE/G-CSF arm and 10.8 months in the CAV/PE arm ($P = 0.103$, difference not significant). The same regimens have also been compared in a phase III National Cancer Institute Canada-Southwestern Oncology Group trial, although intensive CODE was given without G-CSF. This study accrued 202 patients but was terminated early in April 1996 due to the higher toxicity observed in the CODE arm (Murray, personal communication).

The European Organization for Research and Treatment of Cancer is comparing standard CDE with intensified CDE with G-CSF; each arm is subdivided into groups that either are treated with prophylactic antibiotics or are untreated (PDQ data base, NCI). Intensified CDE is delivered every 2 weeks in four cycles. The planned dose intensity will be double that of the standard arm, but the total dose will be the same. A full report of this study is awaited; however, it is anticipated that the difference between the arms will be small.

Stem-cell support

The use of stem-cell support in the treatment of chemosensitive malignancies has been extensively studied, and recent advances in peripheral blood stem-cell transfusion methods have stimulated interest in intensifying the dose in SCLC chemotherapy [6]. However, bone-marrow transplantation trials conducted over the past decade have failed

to demonstrate any benefit for this technique in either the early or the late intensification setting. Although these negative results may be partly due to the lesser effectiveness of the chemotherapy regimens that were available when these studies were conducted, the proportion of elderly SCLC patients is now higher and approximately 65% of patients have extensive disease [11]. Bone marrow and stem-cell harvest is expensive in terms of money and resources, and no randomized controlled trial has compared this modality with standard care. Therefore, this strategy should still be considered experimental.

Conclusions

Neither in terms of the total drug dose given nor in terms of the duration of therapy has maintenance chemotherapy been shown to provide an overall survival benefit. High-dose and dose-intensive chemotherapy has not been proven to have a significant survival benefit, at least to the degree to which dose can currently be intensified. Although stem-cell support may be promising, its indications are limited and it remains experimental. Considering the relatively good condition of the patients enrolled in trials conducted to date, we conclude that more is not better in chemotherapy for SCLC in clinical practice.

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