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Reinduction Chemotherapy in Small Cell Lung Cancer

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Abstract—*Thirteen patients with small cell lung cancer responsive to chemotherapy were retreated with the same regimen at relapse, after a median off-therapy time of 30 weeks. Fifty per cent responded to reinduction; two out of six patients who had complete response to first chemotherapy obtained complete response again at reinduction. Median survival time from start of any therapy was 94 weeks.*

When induction chemotherapy has been effective and of short duration, the same chemotherapy can be attempted again with success at relapse and it may affect survival of relapsing small cell lung cancer patients.

INTRODUCTION

SMALL cell lung carcinoma (SCLC) is well known for developing early and distant metastases, and for being highly sensitive to chemotherapy and radiation. Nevertheless, long-term survival (≥ 30 months from start of therapy) is achieved in less than 20% of patients undergoing aggressive treatment [1].

No improvement of survival of SCLC patients has been attained during the past 5–6 years, despite long and intensive treatment; this has led to the use of shorter and shorter induction regimens, in order to ameliorate the overall quality of survival and prolong time without symptoms and toxicity [2], although optimal therapy length has not been defined yet [3–5].

The shortening of induction chemotherapy has produced a population of patients who receive a relatively small amount of drugs for five to six cycles ± chest radiation and are then followed until relapse.

Second-line chemotherapy in SCLC generally yields disappointing results, with short-lived responses, infrequently observed in over 30–40% of cases, and survival is usually thought not to be influenced by treatment at relapse [6].

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Supposing that short and intensive induction is as active as longer treatments, reinduction with the same chemotherapy, even after a period of suspension of therapy, should not be effective any more and consequently it should not influence survival.

We studied patients who responded to induction and submitted to reinduction with the same regimen at relapse, after having had an off treatment period.

MATERIALS AND METHODS

Among patients entered in three subsequent trials at our Institution employing five to 12 cycles of chemotherapy [3, 7, 8], we looked for those who progressed after having been off therapy for at least 2 months and were then treated with the same initial drug regimen.

From February 1980 to March 1984 132 consecutive patients (95 with local disease and 37 with extensive disease) were treated with VAC (vincristine 1.4 mg/m^2, adriamycin 40 mg/m^2, cyclophosphamide 800–1000 mg/m^2, day 1 every 3 weeks) [7], VAC alternating with cisplatin–VP16-213 (cisplatin 60 mg/m^2 day 1, VP16-213 120 mg/m^2 days 4, 6, 8, alternating with VAC every 3 weeks) [8] or CDE (cyclophosphamide 1000 mg/m^2, day 1, adriamycin 45 mg/m^2, day 1, etoposide 100 mg/m^2, days 1, 3, 5, every 3 weeks) [3] with or without chest irradiation and prophylactic cranial radiotherapy.

Thirteen patients were reinduced (1 with VAC, 4 with cisplatin–VP16.213, and 8 with CDE); their

Table 1. Characteristics and outcome of 13 reinduced patients

No.	EXT/Resp	TFT	Relapse	P.S.	Resp	Duration	Surv 1	Surv 2
1	ED/CR	18	lc	1	CR	22	35	65
2	LD/PR	19	lc	1	NC	14	17	48
3	LD/CR	30	lfn skin	1	CR	19	80	140
3b	— —	—	lfn lc	1	NC	19	60	—
4	LD/PR	29	lfn	2	PD	—	12	94
5	LD/PR	15	lc	1	PR	48	53	69
6	LD/CR	31	cns	2	NC	26	26	69
7	LD/PR	60	lc lung	0	PR	42	75+	185+
8	LD/PR	19	cns	3	PD	—	6	96
9	LD/CR	25	lc li	0	PD	—	8	104
10	LD/CR	78	lc li bo	2	PR	26	28	152
11	ED/CR	30	lc bo cns	3	PR	13	13	67
12	LD/CR	14	cns	2	NE	—	11	37
13	LD/PR	32	li	2	PD	—	9	54

EXT = disease extension; LD = limited disease; ED = extensive disease; Resp = response; CR = complete response; PR = partial response; NC = no change; PD = progression; NE = non-evaluable; TFT = treatment free time (weeks); lc = local; lfn = lymph nodes; cns = central nervous system; li = liver; bo = bone; lung = controlateral lung; P.S. = ECOG performance status; Duration = duration of response to reinduction (weeks); Surv 1 = survival from start of reinduction (weeks); Surv 2 = survival from start of initial chemotherapy (weeks).

features and results of treatment are summarized in Table 1.

RESULTS

Time free from treatment was 14–78 weeks (median 30). Twelve patients overall are evaluable for reinduction results; one patient received only one incomplete reinduction cycle, due to rapid deterioration of general conditions; one patient was reinduced twice.

Responses were: two CR (16.7%), four PR (33.3%), two NC and four PD. Among six evaluable patients who had attained a CR at initial induction two had CR again and two had PR (66.6% response rate), two out of six PR patients obtained PR again at reinduction.

Patient No. 3, who had CR at induction, underwent reinduction twice, obtaining CR again for 19 weeks following first reinduction with VAC chemotherapy, and NC for another 19 weeks after second reinduction with the same regimen. This patient attained again a CR with the use of VM26 (teniposide) on progression.

Toxicity encountered was superimposable on that of initial chemotherapy, except for marrow toxicity, which was more profound during the reinduction period; patient No. 11 died of sepsis during a severe leukothrombocytopenic episode following the administration of the fourth cycle of CDE, despite dose reductions being applied.

Overall median survival from start of reinduction chemotherapy was 26 weeks (range 6–80), and median survival from start of any therapy was 94 weeks (range 37–185+).

DISCUSSION

Treatment has not improved survival of SCLC patients over the past 5–6 years, despite attempts with very aggressive combination chemotherapy ± radiation [1]. The problem of length of treatment has become an important one, having the goal of reducing acute and late toxicity to a minimum. Although the question of optimal treatment length remains unanswered [3–5], it has become common practice in recent years to treat SCLC patients with short and aggressive chemotherapy, followed or not by consolidation (either chemotherapy or radiation) [2, 6].

Bleehen *et al.* did not find any advantage to give six more cycles to patients who responded to the initial six cycles of chemotherapy [4]. In the large ongoing randomized EORTC trial on maintainance chemotherapy no significant difference is apparent in survival between patients treated with five or 12 cycles of CDE, so far [3].

Second-line chemotherapy usually has little impact on survival of SCLC patients who relapse after an aggressive induction, because of the very low response rate. It is unknown, however, if very short inductions might permit second-line chemotherapy to achieve a higher response rate than usual and therefore prolong survival.

Harper *et al.* found a longer survival in patients who had eight cycles instead of four without treatment at relapse, while the relapse chemotherapy regained control in the short course patients [5].

We identified 13 patients who had received prior chemotherapy and were again treated with the same induction regimen, after an off therapy period of at least 2 months. The assumption we made was that

there was some chance of obtaining a new response by reinduction with the initial chemotherapy when response had been unmaintained for at least 2 months. We took into consideration patients who had received either short [3] or intermediate length inductions [7, 8]. A 50% response rate over 12 patients evaluable for response (66.6% in patients who had had CR at induction) was seen, and the reinduction of CR in two of six who had had CR at induction was documented. Patients who initially had PR were less likely to respond again (33.3%). Furthermore, response duration was longer that expected by a second-line trial and 3/13 (23%) patients had a long-term survival.

A median survival of 6 months and 18 months from reinduction and induction starting times, respectively, may be artifically high figures, since patients were selected for favourable prognostic factors (only 2/13 ED patients), response to first-line chemotherapy and long enough survival to undergo a new series of treatment.

Postmus *et al.* recently reported 13 responses out of 23 patients (4 CR + 9 PR) following retreatment with CDE at relapse, at a median of 20 weeks after suspension of induction chemotherapy [9].

Although the reported sample is small, it is interesting and warrants further observation of the phenomenon of reinduction on a larger group of patients treated with a more homogeneous induction regimen.

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