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Perspectives and Commentaries

Intensive Chemotherapy in Small Cell Lung Cancer

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(A COMMENT ON: Postmus PE, Mulder NH, de Vries-Hospers HG *et al.*High dose cyclophosphamide and high dose VP 16-213 for recurrent or refractory small cell lung cancer. A phase II study. *Eur J Cancer Clin Oncol* 1985, **21,** 1467–1470.)

CHEMOTHERAPY has been a major advance in the treatment of small cell lung cancer (SCLC). It has not only resulted in high objective (75–95%) and complete (20–40%) response rates but also and mainly in significantly prolonged survival [1]. However, only a minority of the patients can be considered as cured [2, 3]. Five-year overall survival is about 5% and there are 10 times more long-term survivors in patients with limited disease than in those with disseminated small cell lung cancer. Today results might be improved by new active drugs, development of effective consolidation and/or maintenance treatment, use of more intensive regimens, administration of alternating or sequential combination chemotherapy, adjuvant thoracic irradiation and/or surgery, and/or effective prevention of central nervous system relapses.

Intensive chemotherapy is an attractive approach to improve survival rates, however it results in higher toxicity and thus in a significant toxic death rate. The lethal toxicity is usually grade IV leucopenia (< 1000 white blood cells/mm^3) complicated by severe infections. When so-called "ablative" chemotherapy is used, prolonged marrow aplasia can be shortened by autologous bone marrow transplantation (ABMT). Intensive chemotherapy can be obtained by various types of escalation: increasing the number of active drugs in the combination or the dosage of the administered agents, reducing intervals between courses of chemotherapy and augmenting the total duration of treatment. The goal is to improve killing of lung cancer cells.

A few randomized studies [4–8] have tested the question of whether the addition of a drug to a "standard" regimen can increase response rate and survival (Table 1). Only the trial by Hansen *et al.* performed in extensive disease has shown a survival benefit by adding vincristine to a three-drug combination of CCNU, cyclophosphamide and methotrexate. The other studies have failed to demonstrate survival improvement. However, all but one have obtained a better response rate with the regimen having the higher number of drugs; in that study [8], the addition of etoposide to a cyclophosphamide, adriamycin and vincristine has not resulted in any benefit but, in opposition to the study by Jackson *et al.* [7], the dosage of the "standard" drugs has been reduced in the etoposide-containing regimen. It should be emphasized that these studies have used relatively well tolerated combinations and that no major toxicity has resulted from the addition of another cytostatic agent.

Very few studies [9–11] have compared an identical combination given at different dosage (Table 2); the number of patients included in these trials is small except in the study by Figueredo *et al.* [10]. The study by Cohen *et al.* [9] is often cited and has been a major stimulus for the investigation of intensive chemotherapy; however, the control regimen which was associated with a low response

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Table 1. Randomized studies testing the addition of a drug to a multidrug regimen

Reference	Regimen	Stage	N	OR rate	MST	Analysis
Hansen 1978 [4]	CCNU–CPA–MTX	ED	52	75%	176d	
	vs.					S.
	idem + VCR	ED	53	78%	230d	
Maurer 1980 [5]	CPA–MTX	LD	41	51%	9.0mo	
		ED	40	23%	5.3mo	
	vs.					N.S.
	idem + VCR	LD	47	62%	9.3mo	
		ED	33	36%	5.7mo	
Ettinger 1982 [6]	CCNU + CPA	all	97	28%	21wks	
	vs.					N.S.
	idem + procarbazine	all	95	46%	27wks	
Jackson 1984 [7]	CPA–ADR–VCR	all	67	64%	9.5mo	
	vs.					N.S.
	idem + VP 16	all	68	86%	10.6mo	
Lowenbraun 1984 [8]	CPA–ADR–VCR	ED	52	75%	176d	
	vs.					N.S.
	idem + VP 16	ED	53	78%	230d	

CPA: cyclophosphamide; MTX: methotrexate; VCR: vincristine; ADR: adriamycin; OR: objective response; MST: median survival time; ED: extensive disease; LD: limited disease; d: day; wk: week; mo: month; S: significant; NS: not significant.

rate was clearly underdosed. Two recently reported studies [10, 11] failed to show a survival advantage for the more intensively treated patients, despite an increased objective response rate.

Chemotherapy with megadoses has been tested in various pilot and phase II trials. Administered as a salvage treatment, as recently reported in this journal by Postmus *et al.* [12], it can induce a high rate of objective response but these are unfortunately of short duration. Two different types of approaches can be taken with this kind of very intensive chemotherapy. As shown in Table 3, it can be used as an induction regimen [13–18]. Regimens containing a high dose of cyclophosphamide with or without a dose of etoposide can result in a high rate of complete responses but the median and long-term survivals in these selected groups of patients did not appear to be dramatically improved. A possible advantage of this approach might be the short duration of the treatment period (one to three courses of high dose chemotherapy) contributing to a better quality of life.

Another way to use these intensive regimens is as a consolidation course after that remission has been obtained in order to obtain a larger cell killing at this moment. The few so far reported studies [19–22], have not given encouraging results (Table 4). Some partial responses could be changed into complete remissions but these were usually of short duration. Median and long term survivals are disappointing. The high morbidity and cost of this therapy and the lack of clinical benefits preclude

Table 2. Randomized studies testing dosage of the drugs in the same combination

	Regimens and dosage (mg/m^2)			No	Response rate	CR	PR	MST	Statistical analysis of survival
Cohen 1977 [9]	CCNU	-MTX-	CPA						
	I+II 100	15	1000	23	96%	7	15		not given
	III 50	10	500	9	45%	–	4		
Figueredo 1985 [10]	ADR	-VCR-	CPA						
	I 60	1	1500–2500	52	50%	11	15		NS
	II 50	1	1000	51	39%	11	9		
O'Donnel 1985 [11]	CPA	-VCR-	meCCNU						
	I 2000	2	100	14	43%	3	3	43wk	NS
	II 750	2	75	14	71%	8	2	36wk	

MTX: methotrexate; CPA: cyclophosphamide; ADR: adriamycin; VCR: vincristine; CR: complete response; PR: partial response; MST: median survival time; wk: weeks; NS: not significant.

Table 3. Studies testing megadoses of chemotherapy as induction regimen

	Regimens	Stage	*n*	CR	PR	MST	2 yr survival
Fahra 1983 [13]	CPA + VP16 + VCR + ADR ($4.5g/m^2$)($500mg/m^2$)($3g/m^2$)($80mg/m^2$) + BMT two courses	all	14	54%	46%	56 wk	
Souhami 1983 [14]	CPA (160–200mg/kg) ± BMT one course	mainly LD	25	56%	28%	69 wk	
Souhami 1985 [15]	CPA ± VP16 (200mg/kg)($400–600mg/m^2$) two courses	LD	26	50%	31%	38.6wk	15% (DFS)
Johnson 1985 [16]	CPA + VP16 (100 mg/kg)($1.2g/m^2$) two courses	ED	17	29%	65%	10 mos	
Thatcher 1985 [17]	CPA + VP16 (1.5 to $3.5g/m^2$)($480mg/m^2$) three courses	LD	111	56%	25%	11 mos	13%
Thatcher 1985 [18]	CPA + VP16 ($2.5g/m^2$)($480mg/m^2$) three courses	LD	78	54%	25%	11 mos	

CPA: cyclophosphamide; VCR: vincristine; ADR: adriamycin; CR: complete response; PR: partial response; MST: median survival time; wk: week; yr: year; mo: months; LD: limited disease; ED: extensive disease; BMT: bone marrow transplantation; DFS: disease-free survival.

further development of this approach with presently available drugs.

In conclusion, in SCLC, no study has so far clearly demonstrated a substantial advantage for the so-called intensive chemotherapy, especially regarding the survival.

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Table 4. Studies testing late intensification

	Induction regimen	Late intensification	*n*	PR–CR	MST	3yr DFS
Klastersky 1983 [19]	CDDP–ADR–VP16	CDDP–ADR–VP16 (120)(90 135)(720 1080)mg/m^2 ± BMT	13	1	8.5 mo	1
Smith 1985 [20]	VP16–ADR–VCR	CPA ($7g/m^2$) ± BMT	44	5	10 mo	
Banham 1985 [21]	CPA–ADR–VP16 –VCR–MTX	CPA + VP16 (180 mg/kg)($1g/m^2$) + BMT	22	3	12 mo (LD) 7 mo (ED)	
Sculier 1985 [22]	CPA–ADR–VP16 ± CDDP	CPA + VP16 (100–200mg/kg)(750 to $3.5g/m^2$) ± BMT	16	5	12 mo	1

PR: partial response; CR: complete response; MST: median survival time; 3 yr DFS: 3-year disease-free survival; mo: month; LD: limited disease; ED: extensive disease; CDDP: cisplatin; ADR: adriamycin; VCR: vincristine; CPA: cyclophosphamide; MTX: methotrexate; BMT: bone marrow transplantation.

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