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CLINICAL PRACTICE GUIDELINES

European Lung Cancer Working Party Clinical Practice Guidelines. Small Cell Lung Cancer: V. Extensive disease

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ABSTRACT

The present guidelines on the management of extensive disease small cell lung cancer (SCLC) were formulated by the ELCWP in October 2007. They are designed to answer the following nine questions: 1) What is the definition of extensive disease? 2) What are the active drugs? 3) What is the best induction regimen? 4) Is there a role for maintenance chemotherapy? 5) Is there a role for dose-intensive chemotherapy? 6) Is there a role for the use of haemopoietic growth factors and stem cells support? 7) Is there a role for alternating or sequential chemotherapy? 8) Is there a role for biological treatments? 9) Is there a place for second-line chemotherapy?

INTRODUCTION

This is the fifth of a series of five articles, reporting clinical practice guidelines for lung cancer, formulated by the European Lung Cancer Working Party (ELCWP). These articles consecutively present the recommended treatment of early (resectable) stages of non-small cell lung cancer (NSCLC) (1), locoregionally advanced NSCLC (2), metastatic NSCLC (3) and small-cell lung cancer (SCLC) of limited and extensive stage. The rationale of the reasons and methodology used for those guidelines have been previously reported (1). After an extensive discussion, during a meeting organised in April 2007 in Brussels, Belgium, a consensus was reached among members of the Group to formulate the guidelines of treatment of extensive small cell lung cancer on the basis of nine predefined essential questions:

1. What is the definition of extensive disease?
2. What are the active drugs?
3. What is the best induction regimen?
4. Is there a role for maintenance chemotherapy?
5. Is there a role for dose-intensive chemotherapy?
6. Is there a role for the use of haemopoietic growth factors and stem cells support?

7. Is there a role for alternating or sequential chemotherapy?
8. Is there a role for biological treatments?
9. Is there a place for second-line chemotherapy?

These questions have been extensively discussed during the meeting of April 2007, in Brussels, Belgium. The consensus has been reached definitively approved by the Group in a final meeting in Valencia, Spain, in October 2007.

METHODOLOGY

Guidelines were established on the basis of published data: clinical trials, systematic reviews and meta-analyses, guidelines from medical societies or groups. Literature was identified and analysed by the evidence-based medicine group of the ELCWP. The quality of published guidelines was assessed using the AGREE instrument (4;5), allowing the elimination of the worst ones and the use of the best ones available in the formulation of our own guidelines. The following guidelines were selected: ASCO (American Society of Clinical Oncology) (6;7), BTS (British Thoracic Society) (8), Cancer Care Ontario Practice Guidelines (9;10), Royal College of Radiologists (RCR) (11), American College of Chest Physicians (ACCP) (12;13) and FNCLCC (Fédération Nationale des Centres de Lutte contre le Cancer) (14). Selection was based on the assessment of the literature previously performed by the ACCP (15) and it was completed by the analysis using the AGREE instrument of other guidelines not taken into consideration by the ACCP. This approach allowed adding to the list of guidelines those of FNCLCC and ACCP.

Concerning extensive disease small cell lung cancer specifically, guidelines were available only by Cancer Care Ontario, Royal College of Radiologists and ACCP. Recent evidence-based recommendations have also been performed by the French review Prescrire (16).

QUESTION 1: WHAT IS THE DEFINITION OF EXTENSIVE DISEASE?

Two main systems can be used to define the extent of disease: the International Staging System (ISS) with TNM according to the last version published in 1997 by the UICC (17) or the two-stage system (limited or extensive disease) developed by the Veterans Administration Lung Cancer Study Group (VALCSG) (18). By definition, in any system, extensive disease is a disease which is not limited. In the VALCSG system, patients with limited disease (LD) have tumour involvement restricted to the ipsilateral hemithorax which can be included within a single radiation port. The International Association for the Study of Lung Cancer (19) also includes in the definition of limited disease the presence of contralateral hilar and/or ipsilateral and/or contralateral supraclavicular nodes and/or of pericardial and/or ipsilateral pleural effusion, regardless of the cytology.

In the published so far guidelines, the Royal College of Radiologists (11) defines limited disease as a disease confined to one hemithorax, including involvement of ipsi-and/or contralateral hilar, mediastinal or supraclavicular node while ACCP (20) recommends the use of VALCSG definition. For the ELCWP, the disease should be staged according to both the ISS 97 and the VALCSG definitions. The definition of limited disease should be improved further, taking into account the tumour size and the volume that can be treated according to dose-volume histograms by the current radiotherapy techniques with a tolerable toxicity.

ELCWP GUIDELINES:

The disease should be staged according to both the ISS 97 and the VALCSG definitions, as previously proposed in the ELCWP guidelines for limited disease small cell lung cancer.

QUESTION 2: WHAT ARE THE ACTIVE DRUGS?

No available guidelines define the active drugs against SCLC. Thus, those that have been identified by experts on the basis of the available published trials in the literature, are considered active. They can be divided into three generations: the first generation comprises cyclophosphamide, etoposide, cisplatin, adriamycin, vincristine and methotrexate; the second generation comprises ifosfamide, teniposide, carboplatin, epirubicin and vindesine; and the third generation comprises irinotecan, topotecan and paclitaxel. The activity of gemcitabine, docetaxel, vinorelbine and pemetrexed remains to be confirmed by randomised trials.

Second-generation drugs are mainly analogues of first-generation drugs. Some have been tested in randomised trials: cisplatin versus carboplatin (21;22), etoposide versus teniposide (23), adriamycin versus epirubicin (24). In terms of activity and survival, newer drugs were found no advantageous in any trial.

Several randomised trials aimed to determine the role of third-generation drugs in comparison to regimens using older drugs (table I). Almost all those studies failed to improve the results, no matter if paclitaxel (25-27), irinotecan (28;29) or topotecan (30) were tested.

ELCWP GUIDELINES:

Treatment should be based on the use of established active drugs. The active standard drugs of first and second generations are cyclophosphamide, etoposide, cisplatin, adriamycin, vincristine, methotrexate, ifosfamide, teniposide, carboplatin,

TABLE I. Randomised trials determining the role of third-generation active drugs in the first-line treatment of extensive small cell lung cancer.

Reference	Population	Arm	N	OR	MS	p
Mavroudis, 2001 (25)	1st line, any stage	CDDP 80 +				NS
		I. VP16 80x3 + paclitaxel 175	62	50%	9.5 m	
		II. VP16 120 x 3	71	48%	10.5 m	
Noda, 2002 (28)	1st line, ED	I.CDDP 60 + irinotecan 60 x 3	77	85%	12.8 m	0.002
		II. CDDP 80 + VP16 100 x 3	77	67%	9.4 m	
Reck, 2003 (26)	1st line, any stage	I. Carbo (AUC 5) + VP16 (125) + paclitaxel (175)	305	72%	12.7 m	0.024
		II. Carbo (AUC 5) + VP16 (159) + VCR (2)	309	69%	11.7 m	
Niell, 2005 (27)	1st line, ED	CDDP (80 d1) + VP16 (80 d1-3) +				NS
		-	282	65 %	9.9 m	
		paclitaxel (175 J1) + GCSF	283	73 %	10.6 m	
Eckardt, 2006 (30)	1st line, ED	I. topotecan oral + cisplatin (60)	389	63 %	39.3 w	NS
		II. cisplatin (80) + etoposide	305	69 %	40.3 w	
Hanna, 2006 (29)	1st line, ED	I. irinotecan + cisplatin (30 x 2)	221	48 %	9.3 m	NS
		II. cisplatin (60) + etoposide	110	44 %	10.2 m	

N: number; OR: objective response; MS: median survival; NS: non significant; m: month; w: week; ED: extensive disease; CDDP: cisplatin; carbo: carboplatin; VP16: etoposide

epirubicin and vindesine. The new active drugs are irinotecan, topotecan and paclitaxel.

QUESTION 3: WHAT IS THE BEST INDUCTION REGIMEN?

The RCR (11) does not recommend any particular regimen among those that are most frequently used: PE (cisplatin + etoposide), CAV (cyclophosphamide + adriamycin + vincristine), CDE (cyclophosphamide + adriamycin + etoposide). The ACCP (31) recommends a platinum-based chemotherapeutic regimen, with either etoposide or irinotecan (Simon II) and the evidence-based medicine review Prescrire (16) recommends the cisplatin plus etoposide combination.

The level of evidence is two meta-analyses. In the first one (32), the role of cisplatin and etoposide was assessed by a systematic review of the literature. Thirty-six trials were eligible for a total of 7,173 patients. Overall survival was significantly improved when etoposide was given (HR: 0.73; 95% CI: 0.67-0.78; 17 trials), when cisplatin was added to etoposide (HR: 0.74; 95% CI: 0.66-0.83; 9 trials) or when the cisplatin plus etoposide regimen was administered (HR: 0.57; 95% CI: 0.51-0.64; 9 trials). In the second one (33), including 9 trials with 1,579 evaluable patients, the addition of cisplatin significantly improved 6 month (OR: 0.87; 95% CI: 0.78-0.98) and 1 year (OR: 0.80; 95% CI: 0.69-0.93) survival rates.

It should be noted that there are only two published trials comparing cisplatin to carboplatin, one in association with etoposide (21) and the other with teniposide and vincristine (22). In both studies, there was no statistical difference between the arms in terms of response and survival.

The newer drugs have been so far unable to improve the survival results obtained with cisplatin plus etoposide (table I). The addition of paclitaxel to that combination failed to improve survival (25;27). Cisplatin plus topotecan (30) or irinotecan (29) were not better than cisplatin plus etoposide, despite a preliminary promising but unconfirmed trial (28).

ELCWP GUIDELINES:

Cisplatin plus etoposide should be used as first-line induction chemotherapy. Evidence is too limited to substitute carboplatin for cisplatin. Alternatively, if cisplatin can not be administered, the regimen should include etoposide.

QUESTION 4: IS THERE A ROLE FOR MAINTENANCE CHEMOTHERAPY?

The RCR (11) recommends no maintenance treatment

and a maximum of 6 courses. For ACCP (34), maintenance chemotherapy has no indication outside the context of a clinical trial.

Level of evidence is based on 15 randomised trials (table II), a systematic review of the literature and a meta-analysis. In the systematic review performed by the ELCWP (35), randomised trials provided apparently contradictory results. In fact, there was a high heterogeneity between studies, both in their design (consolidation, maintenance or only further chemotherapy cycles; type of drugs used) and in their methodology (such as lack of definition of the primary objective or of the a priori estimate of the sample size necessary to conduct the trial). It was concluded that a quantitative aggregation of such heterogeneous trials was meaningless. Nevertheless, the systematic review provides some indications in favour of the maintenance/consolidation chemotherapy such as for example 2 cycles of cisplatin-etoposide after obtaining complete response with CAV or further cycles with that regimen when an objective response is obtained (35). The problem is that the majority of these studies were performed with regimens that are obsolete today. Nevertheless, a Turkish team performed a meta-analysis (36), showing significant 1-year (OR: 0.67; 95% CI: 0.56-0.79; 14 trials) and 2-year (OR: 0.67; 95% CI: 0.53-0.89) survival improvement by maintenance treatment.

The two most recent trials showed significantly increased progression-free survival when oral topotecan (37) or oral etoposide (38) was given after 4 cycles of cisplatin-etoposide based chemotherapy.

ELCWP GUIDELINES:

Maintenance chemotherapy trials gave conflicting results. So far, there is no indication for maintenance after induction by cisplatin plus etoposide. Chemotherapy should consist in at least 4 to 6 courses of induction chemotherapy in responding patients.

QUESTION5: IS THERE A ROLE FOR DOSE-INTENSIVE CHEMOTHERAPY (WITHOUT THE USE OF HAEMOPOIETIC GROUTH FACTORS)?

In their guidelines, the RCR (11) and the ACCP (39) both state that there is no role for dose-intensive chemotherapy in

TABLE II. Randomised trials testing maintenance chemotherapy.

Reference	Population randomised	CT induction	N cycles	CT maintenance	N cycles	nb pts	PFS	survival
Maurer, 1980 (58)	CR	CPA or CMV	6	cf induction	until relapse	47	NS	(S)
Cullen, 1986 (59)	OR	VAC	6	cf induction	8	61	?	(S)
Einhorn, 1988 (60)	OR	VAC	6	CDDP-VP16	2	151	S	S
MRC, 1989 (61)	OR	VP16-CPA-MTX-VCR	6	cf induction	6	265	?	(S)
Spiro, 1989 (62)	initial	CPA-VCR-VP16	4	cf induction	4	610	S	(S)
Byrne, 1989 (63)	initial	CDDP-VP16´CMV	3 x 2	CMV	6	66	NS	NS
Ettinger, 1990 (47)	CR	VAC ± HMM-VP16-MTX	6-8	cf induction	20-22	86	(S)	NS
Mattson, 1992 (64)	OR	CPA-VCR-VP16 + RT	4	CPA-CDDP-ADR	6	146	?	NS
Lebeau, 1992 (65)	CR	CCNU-CPA-ADR-VP16	6	cf induction	6	79	NS	NS
Giaccone, 1993 (66)	No progression	ADR-VP16-CPA	5	cf induction	7	434	S	NS
MRC, 1993 (67)	initial	VP16-CPA-MTX-VCR	3	cf induction	3	309	?	NS
Sculier, 1996 (68)	OR	Ifo-VP16-ADR or epir	6	VP16-VDS	12	91	S	(S)
Beith, 1996 (69)	OR	CDDP-VP16 + RT	4	VAC	10	129	NS	NS
Schiller, 2001 (37)	OR & NC	CDDP-VP16	4	Topotecan	4	223	S	NS
Hanna, 2002 (38)	OR & NC	CDDP-VP16 - Ifo	4	oral VP16	3	144	S	0.07

N: number; OR: objective response; CR: complete response; PFS: progression-free survival; NS: non significant; S: significant; CT: chemotherapy; CDDP: cisplatin; VP16: etoposide; CPA: cyclophosphamide; Ifo: ifosfamide; ADR: adriamycin; VCR: vincristine; epir: epirubicin; MTX: methotrexate; HMM: hexamethylmelamine; RT: radiotherapy; CMC: CPA-MTX-VCR; VAC: CPA-ADR-VCR

the management of SCLC.

The level of evidence is derived from randomised clinical trials testing various modalities to provide more intensive chemotherapy: increase of the number of active drugs in the combination, increase of the dose of one or more administered drugs, weekly chemotherapy administration, increased relative dose-intensity (RDI) for a same total cumulative dose (dose-dense or concentrated chemotherapy), use of haemopoietic growth factors (see question 7).

The effect of the addition of one or two drugs to a basic combination (table III) has been tested in 23 randomised trials. Only 4 have shown a benefit in terms of survival and

TABLE III-A. Randomised clinical trials testing the increase in the number of active drugs in the combination.

Reference	Chemotherapy	stage	n pts	OR	p	MS	p
Edmonson, 1976 (70)	1. CPA 2. + CCNU	all	118 110	22% 43%	NA	17.1 w 11.7 w	NA
Hansen, 1978 (71)	1. CCNU-CPA-MTX 2. + VCR	ED	52 53	75% 78%	NS	176 d 230 d	S
Maurer, 1980 (58)	1. CPA-MTX 2. + VCR	LD ED LD ED	41 40 47 33	51% 23% 62% 36%	NA	9.0m 5.3m 9.3m 5.7m	NS
Ettinger, 1982 (72)	1. CCNU-CPA 2. + PCZ	all	97 95	28% 46%	NA	21 w 27 w	NS
Jackson, 1984 (73)	1. CPA-ADR-VCR 2. + VP16	all	67 68	64% 86%	S	9.5m 10.6m	NS
Lowenbraun, 1984 (74)	1. CPA-ADR-VCR 2. + VP16	ED	148 145	72% 74%	NS	42.1 w 42.3 w	NS
Zhiyi, 1984 (75)	1. CPA-ADR-5FU 2. + PCZ	all	19 19			68 w 68 w	NS
Messeih, 1987 (76)	1. CPA-ADR-VCR 2. + VP16	all	49 43	50% 65%	NS	36 w 45 w	NS
Jackson, 1988 (77)	1. CPA-ADR-VCR 2. + VP16	ED	68 71	46% 70%	S	7.8m 9.4m	NS
Niiranen, 1989 (78)	1. CPA-VCR 2. + MTX-CCNU	LD	29 26	46% 56%	NS	12m 16m	NS
Jett, 1990 (79)	1. CPA-ADR-VCR 2. + VP16	LD	113 118	83% 84%	NS	12.4m 15.1m	NS
Sculier, 1990 (80)	1. VP16-VDS 2. + CDDP	all	106 95	55% 74%	S	40 w 45 w	NS
Nikkanen, 1990 (81)	1. CPA-ADR-VCR 2. + VP16	LD	41 39	84% 75%	NS	10 m 14 m	NS
Smith, 1991 (82)	1. VCR-ADR-CPA-VP16 2. + CDDP	all	48 47	65% 72%	NS	47 w 40 w	NS
Miyamoto, 1992 (83)	1. CDDP-VP16 2. + Ifo	All	45 47	78% 74%	NS	55 w 56 w	NS

N: number; OR: objective response; MS: median survival; NA: non available; NS: non significant; m: month; w: week; d: days; ED: extensive disease; LD: limited disease; NS: non significant; S: significant; CT: chemotherapy; CDDP: cisplatin; carbo or CBDCA: carboplatin; VP16: etoposide; CPA: cyclophosphamide; Ifo: ifosfamide; ADR: adriamycin; VCR: vincristine; VDS: vindesine; 5FU: 5-fluorouracil; MTX: methotrexate; PCZ: procarbazine; PAC: paclitaxel

TABLE III-B. Randomised clinical trials testing the increase in the number of active drugs in the combination.

Reference	Chemotherapy	Stage	n pts	OR	p	MS	p
Gatzemeier, 1994 (84)	1. VP16-VCR 2. + CBDCA	ED	173 171	60% 80%	S	9 m 10 m	NS
Loehrer, 1995 (85)	1. CDDP-VP16 2. + Ifo	ED	84 87	67% 73%	NS	7.3 m 9.1 m	S
MRC, 1996 (86)	1. VP16-VCR 2. + CPA-MTX	All	156 154	46% 40%	NS	137 d 141 d	NS
Urban, 1999 (49)	1. CPA-ADR-VP16 2. + CDDP	all	228 229	52% 72%	S	266 d 271 d	NS
Hirsch, 2001 (87)	1. Carbo + CDDP + VM26 + VCR then CPA + epirubicin 2. Idem without CDDP	all LD ED all LD ED	140 67 68 149 74 60	71 78 67 72 69 75		314 d 417 d 232 d 294 d 327d 233 d	 S NS
Pujol, 2001 (88)	1. CDDP-VP16 2. Idem + CPA-epirubicine	ED	109 117	61 76	NS	9.3 m 10.8 m	0.006
Mavroudis, 2001 (25)	CDDP 80 + I. VP16 80x3 + PAC 175 II. VP16 120 x 3	all	 62 71	 50% 48%		 9.5 m 10.5 m	NS
De Marinis, 2005 (89)	CDDP + gemcitabine 1. - 2. + VP16	ED	 70 70	 57% 63%	NS	 10m 9.5m	NS

N: number; OR: objective response; MS: median survival; NA: non available; NS: non significant; m: month; w: week; d: days; ED: extensive disease; LD: limited disease; NS: non significant; S: significant; CT: chemotherapy; CDDP: cisplatin; carbo or CBDCA: carboplatin; VP16: etoposide; CPA: cyclophosphamide; Ifo: ifosfamide; ADR: adriamycin; VCR: vincristine; VDS: vindesine; 5FU: 5-fluorouracil; MTX: methotrexate; PCZ: procarbazine; PAC: paclitaxel

5 in terms of response rate. In fact, most studies are biased because drug doses have been reduced in the regimen when a new drug was added. The impact of drug dose augmentation in a given combination (table IV) has been tested in 8 randomised trials, all presenting methodological problems or using parallel endpoints. Weekly chemotherapy (table V) has been investigated in 6 randomised trials, without showing significant advantage in terms of survival and response. Often, weekly chemotherapy was associated with a diminution of dose-intensity. Dose-dense chemotherapy (table VI), providing an increased RDI for a same total cumulative dose, has been tested in two randomised trials, including one with deleterious effect (40).

Dose-intensive chemotherapy can also be provided with the use of haemopoietic growth factors. That aspect will be discussed in the next question.

ELCWP GUIDELINES:

There is no evidence in favour of dose-intensive chemotherapy, whatever the modality.

QUESTION 6: IS THERE A ROLE FOR THE USE OF HAEMOPOIETIC GROWTH FACTORS AND STEM CELLS SUPPORT?

The only guideline on the topic, made by the ACCP (41), does not recommend the routine use of G-CSF.

The level of evidence is derived from multiple randomised clinical trials and a meta-analysis. Haemopoietic growth factors can be used for four purposes: maintenance of dose-intensity through neutropenia diminution, acceleration of chemotherapy, administration of dose-dense chemotherapy (concentration) and use of megadose chemotherapy (with stem cells support).

For the maintenance of dose-intensity, the evidence comes from secondary endpoint analyses of randomised trials performed in order to reduce neutropenia and thus to diminish

TABLE IV. Randomised clinical trials testing drug dose increase

Reference	Chemotherapy with dosage (mg/m²)	Stage	nb pts	OR	p	MS	p
Cohen,	CCNU-MTX- CPA	all			NA		NA
1977 (90)	1. 100 15 1000		23	96%			
	2. 50 10 500		9	45%			
Figueredo,	ADR-VCR-CPA	all			NS		NS
1985 (91)	1. 60 1 1500-2000		52	71%			
	2. 50 1 1000		51	61%			
O'Donnell,	CPA- VCR- meCCNU	all			NS		NS
1985 (92)	1. 2000 2 100		14	43%		43 w	
	2. 750 2 75		14	72%		36 w	
Wolf,	VP16 J1-3	All pretreated			NS		NS
1986 (93)	1. 100		26	4%		12.6 w	
	2. 200		27	7%		20.0 w	
	3. 300		26	4%		22.5 w	
Johnson,	CPA-ADR-VCR	ED			S		NS
1987(94)	1. 1200 70 1		101	64%		29.3 w	
	2. 1000 40 1		146	53%		34.7 w	
Arriagada,	CPA-CDDP-ADR-VP16 (!1st course only)	LD		(CR)	NS	2 yrs	S
1993 (95)	1. 1200 100 40 225		51	67%		43%	
	2. 900 80 40 225		48	54%		26%	
Ihde,	CDDP – VP16	ED			NS		NS
1994 (96)	1. 135 400		44	86%		11 m	
	2. 80 240		46	83%		10 m	
Pujol,	CPA-Epir-VP16-CDDP	ED			NS		S
1997(40)	1. 1800 60 330 120		65	87%		8.9 m	
	2. 1200 40 225 100		60	74%		11 m	

N: number; OR: objective response; CR: complete response; MS: median survival; NA: non available; NS: non significant; m: month; w: week; yr: year; ED: extensive disease; LD: limited disease; NS: non significant; S: significant; CDDP: cisplatin; VP16: etoposide; CPA: cyclophosphamide; ADR: adriamycin; VCR: vincristine; MTX: methotrexate; epir: epirubicine.

the risk of infectious complications (table VII). Those trials failed to show significant effect on response rate and survival, despite better delivered dose-intensity with the growth factors. The results have been confirmed by an *ad hoc* meta-analysis of the literature (42) with a survival HR of 1.004 (95% CI: 0.89-1.13).

Accelerated chemotherapy (table VIII) has also failed to improve survival in all but one trials. The meta-analysis did not show a significant effect (42). As mentioned above, dose-dense (concentration) chemotherapy, with the purpose to increase RDI for a same total cumulative dose, failed to improve results (table VI). There was even a deleterious trial (40). Megadose chemotherapy with the support of blood-progenitors-cell support has been the topic of two randomised trials (table IX), one as late consolidation (43) and another as induction chemotherapy (44). That modality failed also to improve results.

ELCWP GUIDELINES:

There is no evidence for improved survival by using haemopoietic growth factors or stem cells support to increase or to maintain dose-intensity, whatever the proposed modality.

QUESTION 7: IS THERE A ROLE FOR ALTERNATING OR SEQUENTIAL CHEMOTHERAPY?

Alternating chemotherapy consists in cycles of two chemotherapy regimens A and B in the following way ABABAB while sequential chemotherapy provides them successively as AAABBB. That concept has been investigated in multiple randomised clinical trials summarised in table X. When better results were obtained, they can easily be explained by the use of better drugs in the improved arm, such as cisplatin and etoposide (45-49).

TABLE V. Randomised clinical trials testing weekly chemotherapy

Reference	Chemotherapy	Stage	nb pts	OR	p	MS	p	RDI
Sculier, 1993 (97)	1. ADR-VP16-CPA~ CDDP-VDS~MTX-VCR 2. ADR-CPA-VP16	all	107 108	69% 61%	NS	49 w 43 w	NS	71% 85%
Souhami, 1994 (98)	1.CDDP-VP16~Ifo-ADR 2.CDDP-VP16~VAC	all	221 217	82% 81%	NS	11 m 11 m	NS	73% 93%
James, 1996 (99)	1.CDDP-VP16~VAC 2.CDDP-VP16´VAC	all	78 89	59% 45%	NS	6 m 6 m	NS	87% 90%
Furuse, 1998 (100)	1.CDDP-VP16~VAC 2.CODE + G-CSF (CDDP-ADR-VP16-VCR)	ED	113 114	76% 85%	NS	11 m 12 m	NS	82% 72%
Murray, 1999 (101)	1. CODE 2. CAV ~ CDDP-VP16	ED	110 109	87% 70%	S	0.98 yr 0.91 yr	NS	
Sekine, 2003 (102)	CDDP-VP16-Irinotecan 1.weekly 2.monthly	ED	 30 30	 80% 67%		 8.9 m 12.9 m		

N: number; OR: objective response; RDI: relative dose-intensity; MS: median survival; NS: non significant; m: month; w: week; yr: year; ED: extensive disease; NS: non significant; S: significant;; CDDP: cisplatin; VP16: etoposide; CPA: cyclophosphamide; ADR: adriamycin; VCR: vincristine; MTX: methotrexate;; Ifo: ifosfamide; VAC: CPA-ADR-VCR; CODE: CDDP + VCR + ADR + VP16

TABLE VI. Randomised clinical trials testing dose-dense or concentration chemotherapy.

Reference	Chemotherapy (mg/m²)	Stage	nb pts	OR	p	MS	p
Pujol, 1997 (40)	CPA-Epir-VP16-CDDP 1. 1800 60 330 120 + GM 2. 1200 40 225 100	ED	 65 60	 87% 74%	NS	 8.9 m 11 m	S
Ardizzoni, 2002(103)	CPA-ADR-VP16 1. 1 45 300 2. 1,2 55 375 + G	any	 119 125	 79% 84%	NS	 54 w 52 w	NS

N: number; OR: objective response; MS: median survival; NS: non significant; m: month; w: week; ED: extensive disease; NS: non significant; S: significant; CDDP: cisplatin; VP16: etoposide; CPA: cyclophosphamide; ADR: adriamycin; Epir: epirubicine

ELCWP GUIDELINES:

There is no evidence in favour of the use of alternating or sequential chemotherapy.

QUESTION 8: IS THERE A ROLE FOR BIOLOGICAL TREATMENT?

Randomised clinical trials have tested interferons, anticoagulants/antiaggregatants and metalloproteinase inhibitors.

Interferons, either administered as maintenance or as induction together with chemotherapy, have failed to provide better results (table XI). In addition, they were associated with significant toxicity.

Anticoagulants (heparin, warfarin) and antiaggregatants (aspirin) (table XII) have been associated with potentially interesting results in a trial with heparin given during the first 5 weeks of induction chemotherapy (50).

Marimastat, a metalloproteinase inhibitor, given as consolidation after remission obtained by chemotherapy, has failed to improve survival (51).

ELCWP GUIDELINES:

There is no evidence in favour of the use of biological treatments for routine application. Anticoagulants merit further investigations.

QUESTION 9: IS THERE A PLACE FOR SECOND LINE CHEMOTHERAPY?

For ACCP (52), the second-line chemotherapy will depend on the lack of response to first-line chemotherapy (sensitive

TABLE VII. Randomised clinical trials testing the maintenance of dose-intensity with the use of haematopoietic growth factors.

Reference	Regimen	N pts	OR	p	MS	p
Crawford, 1991(104)	ACE Idem + G	199	80% 72%	NS	12 m 11 m	NS
Trillet, 1993 (105;106)	ACE Idem + G	130	87% 79%	NS	12 m 11 m	0.27
Hamm, 1994 (107)	ACE Idem + GM	233	86% 75%	NS		0.8
Bunn, 1995 (108)	CDDP-VP16 Idem + GM	230	86% 73%	NS	17 m 14 m	0.15
Steward, 1998 (109)	VICE Idem + GM	98	77% 78%	NS		
Fukuoka, 1997 (110)	CODE Idem + G	63	84% 97%	0.07	8 m 15 m	0.004
Gatzemeier, 2000 (111)	ACE Idem + G	280	79% 76%	NS	10 m 11 m	NS

N: number; OR: objective response; MS: median survival; NS: non significant; m: month; NS: non significant; CDDP: cisplatin; VP16: etoposide; CPA: cyclophosphamide; ADR: adriamycin; VCR: vincristine; CODE: CDDP + VCR + ADR + VP16; ACE: CPA + ADR + VP16; G: G-CSF; GM: GM-CSF; VICE: VCR + ifosfamide + CDDP + VP16

relapse versus refractory patients) or on the response duration after first-line chemotherapy. For the Ontario Cancer Care Programme (53), the selection of patients should be dependent on the treatment-free interval, the extent of response to first-line chemotherapy, the residual toxicity from first-line chemotherapy and the performance status of the patient. There is insufficient evidence to recommend a specific chemotherapy regimen. According to *Prescrire* (16), there is no particular second-line chemotherapy regimen to be recommended.

There is only one randomised clinical trial comparing supportive care only with chemotherapy using single-agent oral topotecan (54). Survival was significantly improved with active treatment (Table XIII). In another trial (55), that drug was no better than the VAC regimen (vincristine + adriamycin + cyclophosphamide). Two other small randomised trials are also available for salvage chemotherapy (56;57).

ELCWP GUIDELINES:

Second-line chemotherapy is associated with a small improvement in survival. If relapse occurs after a response to the first-line chemotherapy with a chemotherapy-free interval of more than 3 months, the tumour can be considered still sensitive. In the other situations, the only active combination is cisplatin-etoposide for patients with no prior exposure to these drugs. No other chemotherapy regimen can be specifically recommended.

TABLE VIII. Randomised clinical trials testing accelerated chemotherapy.

Reference	chemotherapy	stage	n pts	OR %	p	MS	p	RDI %	p
Miles, 1994 (112)	CDDP-VP16/Ifo-ADR 1. accelerated-CSF 2. accelerated	all	23 17	74 71	NS	? ?		84 82	NS
Woll, 1995 (113)	VCR-Ifo-CBDCA-VP16 1. accelerated +G-CSF 2. accelerated	all	34 31	94 93	NS	69 w 64 w	NS	134 117	S
Steward, 1998 (109)	CBDCA-VP16-Ifo-VCR 1. accelerated +/- GM-CSF(q3 wks) 2. non accelerated +/- GM-CSF (q4wks)	all	147 153	90 77	NS	443 d 351 d	S	126 100	ND
Thatcher, 2000 (114)	CPA – ADR – VP16 1. q2wks + G-CSF 2. q3wks	all	201 202	79 78	NS		0.04	95 85	
Woll, 2001 (115)	Ifo + Carbo + VP16 1. standard 2. accelerated + G-CSF	all	50	76 80	NS	12 m 12 m	0.89		
Sculier, 2001 (116)	Ifo + VDS + epirubicine 1. standard 2. accelerated + GM-CSF 3. accelerated+ cotrimoxazole	ED	78 78 77	59 76 70	0.04	286 d 264 d 264 d	0.86	93 90 65	<0.001

N: number; OR: objective response; RDI: relative dose-intensity; MS: median survival; NS: non significant; m: month; w: week ED: extensive disease; NS: non significant; S: significant;; CDDP: cisplatin; VP16: etoposide; CPA: cyclophosphamide; ADR: adriamycin; VCR: vincristine; Ifo: ifosfamide; VDS: vindtsine; CBDCA or carbo: carboplatine

TABLE X. Randomised clinical trials testing alternating or sequential chemotherapy.

Reference	chemotherapy	arm	stage	nb pts	OR %	MS	p
Chak, 1982 (117)	A: PCZ-VCR-CPA-CCNU B: VP16-ADR-MTX	A B~A	all	85 76			NS
Osterlind, 1983 (118)	A: BCNU-CPA-VCR-MTX B: ADR-VP16	A A~B	ED	76 70	68 72	36 w 38 w	NS
Daniels, 1984 (119)	A: CPA-VCR-PCZ-CCNU B: VP16-ADR-MTX	A A~B	all	84 78	53 63		NS
Livingston, 1984 (120)	A: VCR-MTX-VP16 B: VAC	A B A~B	ED	146 155 144	58 60 64	28 w 31 w 33 w	NS
Maurer, 1985 (121)	A: MTX-ADR-CPA-CCNU B: CCNU-CPA-VCR C: ADR-VCR	A B~C	LD	157 150	74 72	12m 12m	NS
Havemann 1987 (45)	A: CCNU-ADR-VCR B:VP16-VDS-Ifo C:CPA-MTX-CCNU	A A~B~C	all	152 150	59 70	10m 11m	S
Evans, 1987 (46)	A: VAC B: CDDP-VP16	A A~B	ED	144 145	63 80	8m 10m	S
Feld, 1987 (122)	A: VAC B:CDDP-VP16	A~B 3A→3B	LD	154 146	82 77	62w 60w	NS
Chahinian, 1989 (123)	A: MTX-ADR-CPA-CCNU B: MMC-VP16-CDDP-HMM	A A~B	ED	86 105	51 48	8m 8m	NS
Havemann, 1989 (124)	A: Ifo-VP16 B: VAC	A A~B	all	161 165	75 59	10m 10m	NS
Goodman, 1990 (125)	A: VP16-CPA-ADR-VCR B: CDDP-VP16 C: VAC	A B~C	LD	199 201	68 72	15m 17m	NS
Ettinger, 1990 (47)	A: VAC B: HMM-VP16-MTX	A A~B	ED	294 283	61 64	43w 46w	S
Fukuoka, 1991 (48)	A: VAC B: CDDP-VP16	A B A~B	all	97 97 94	55 78 76	10m 10m 12m	(S)
Wolf, 1991 (126)	A: Ifo-VP16 B: VAC	A A~B	all	162 159	77 70	11m 10m	NS
Wampler, 1991 (127)	A: VAC B: MTX-CDDP-VP16	A B~A	ED	79 82	54 53	7m 9m	NS
Roth, 1992 (128)	A: CDDP-VP16 B: VAC	A B A~B	ED	148 146 143	61 51 60	9m 8m 8m	NS
Joss, 1994 (129)	A: ADR-CDDP-VP16 B: CPA-VP16-ADR C: MTX-VCR-CPA	A B C~A	all	92 86 88	80 56 88	319d 265d 288d	NS
Joss, 1995 (130)	A: CDDP-ADR-VP16 B: CPA-MTX-VCR-CCNU	A~B 3A→3B	tall	202 204	88 87	339d 371d	(S)
Postmus, 1996 (131)	A: CPA-ADR-VP16 B: VCR-CBDCA-Ifo	A A~B	ED	75 73	68 70	8m 9m	NS
Urban, 1999 (49)	A: CCNU-CPA-ADR-VP16 B: CCNU-ADR ~CDDP-VDS-VP16	A x 6 B 3x2	all	223 191	78 64	306d 272 d	0.08

N: number; OR: objective response; MS: median survival; S: significant; NS: non significant; m: month; w: week; d: days; ED: extensive disease; LD: limited disease; CDDP: cisplatin; carbo or CBDCA: carboplatin; VP16: etoposide; CPA: cyclophosphamide; Ifo: ifosfamide; ADR: adriamycin; VCR: vincristine; VDS: vindesine; MMC: mitomycin C; HMM: hexamethylmelamine; MTX: methotrexate; PCZ: procarbazine; VAC: CPA-ADR-VCR.

TABLE IX. Randomised clinical trials testing megadosage chemotherapy

Reference	chemotherapy	nb pts	OR %	p	MS	p
Humblet, 1987(43)	1. Standard 2. Late intensification with autoBMT	22 23			55 w 68 w	NS
Lorigan, 2005 (44)	1. Standard: Ifo (5) – Carbo (300) – VP16 (180 x 2) q4 wks 2. Intensified: Ifo (5) – Carbo (300) – VP16 (180 x 2) q2 wks with filgrastine and PBCs	159 159	88% 89%	0.09	13.9 m 14.4 m	NS

N: number; OR: objective response; MS: median survival; NS: non significant; m: month; w: week NS: non significant; BMT: bone marrow transplantation; VP16: etoposide; carbo: carboplatine; PBC: progenitor blood cell

TABLE XI. Randomised clinical trials testing interferons.

Reference	chemotherapy	IFN	modality	stage	nb pts	MS CT	MS CT + IFN	p
Mattson, 1992 (64)	CPA-VCR-VP16	α 6 m	maintenance	all	237	11m	11m	NS
Jett, 1994 (132)	CDDP-VP16	γ 6 m	maintenance CR	all	100	19m	13m	NS
Kelly, 1995 (133)	CDDP-VP16 + RT	α 2 yrs	maintenance OR	LD	133	10m	9m	NS
Zarogoulidis, 1996 (134)	CBDCA-Ifo-VP16	α CT	induction 6-8 m	all	45	11m	10m	NS
van Zandwijk 1997 (135)	various	γ 4 m	maintenance CR	all	120	10m	9m	NS
Prior, 1997 (136)	VAC~CDDP-VP16	α 6 m	induction 6 m	all	77	9m	11m	0.02
Ruotsalainen, 1999 (137)	CDDP-VP16	I. α RC II. α Roche	induction	all	219	10 m	10 m 10 m	NS

N: number; OR: objective response; CR: complete response; CT: chemotherapy; IFN: interferon; MS: median survival; NS: non significant; m: month; yr: year; LD: limited disease; CDDP: cisplatin; CBDCA: carboplatin; VP16: etoposide; CPA: cyclophosphamide; Ifo: ifosfamide; ADR: adriamycin; VCR: vincristine; VAC: CPA-ADR-VCR.

TABLE XII. Randomised clinical trials testing anticoagulants/antiaggregatants

Reference	chemotherapy	anticoagulant/ antiaggregant	modality	stage	nb pts	MS CT	MS CT + anti	p
Chahinian, 1989 (123)	MTX-ADR-CPA-CCNU	warfarine	induction	ED	189	8m	9m	NS
Lebeau, 1993 (138)	CPA-CCNU-ADR-VP16	aspirine	induction 18 m	all	303	285d	282d	NS
Lebeau, 1994 (50)	CPA-ADR-VP16-CCNU	heparine SC	induction 5 w	all	277	261d	317d	0,01
Maurer, 1997 (139)	ADR-CPA-VP16	warfarine	induction 6 m	LD	369	19m	21m	NS

N: number; MS: median survival; S: significant; NS: non significant; m: month; w: week; d: days; ED: extensive disease; LD: limited disease; CT: chemotherapy; anti: anticoagulants/antiaggregants; VP16: etoposide; CPA: cyclophosphamide; ADR: adriamycin; MTX: methotrexate.

TABLE XIII. Randomised clinical trials testing salvage chemotherapy.

Reference	Population	Arm	N pts	OR	MS	p
von Pawel, 1999 (55)		I. Topotecan	107	24%	25w	NS
		II. VCR-ADR-CPA	104	18%	25w	
von Pawel, 2001 (56)	chemo-sensitive (FI >3m)	Topotecan				NS
		I. 2.3 mg/m^2 po d1-5	52	23%	32w	
		II. 1.5 mg/m^{2}IV d1-5	54	15%	25w	
Sculier, 2002 (57)		CDDP (60 mg/m^2) + VP16+				NS
		I. –	31	29%	4.3 m	
		II. Carboplatin (200 mg/m^2)	34	47%	7.6 m	
O'Brien, 2006 (54)		Topotecan oral	71	7%	25.9w	0.01
		Supportive care	70		13.9w	

N: number; MS: median survival; OR: objective response; NS: non significant m: month; w: week; d: days; VP16: etoposide; CPA: cyclophosphamide; ADR: adriamycin; VCR: vincristine; CDDP: cisplatin; FI: free interval.

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