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CLINICAL PRACTICE GUIDELINES

European Lung Cancer Working Party Clinical Practice Guidelines. Non-small cell lung cancer: III. Metastatic Disease

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ABSTRACT

The present guidelines on the management of advanced non-small cell lung cancer (NSCLC) were formulated by the ELCWP in October 2006. They are designed to answer the following twelve questions: 1) What benefits can be expected from chemotherapy and what are the treatment objectives? 2) What are the active chemotherapeutic drugs for which efficacy has been shown? 3) Which are the most effective platinum-based regimens? 4) Which is the indicated dosage of cisplatin? 5) Can carboplatin be substituted for cisplatin? 6) Which is the optimal number of cycles to be administered? 7) Can non-platinum based regimens be substituted for platinum based chemotherapy as first-line treatment? 8) Is there an indication for sequential chemotherapy? 9) What is the efficacy of salvage chemotherapy and which drugs should be used in that indication? 10) What is the place of targeted therapies? 11) What is the place of chemotherapy in the management of a patient with brain metastases? 12) Which specific drugs can be used for the patient with bone metastases?

INTRODUCTION

This is the third of a series of five articles, reporting clinical practice guidelines for lung cancer, formulated by the European Lung Cancer Working Party (ELCWP). The articles consecutively present the recommended treatment of early (resectable) stages of non-small cell lung cancer (NSCLC) [1], locoregionally advanced NSCLC [2], metastatic NSCLC and small-cell lung cancer (SCLC) of limited and extensive stage. The rational of the reasons and methodology used for those guidelines has been previously reported [1].

After an extensive discussion, a consensus was reached among members of the Group to formulate the guidelines of treatment of advanced stages of non-small lung

cancer on the basis of twelve predefined essential questions: 1) What benefits can be expected from chemotherapy and what are the treatment objectives? 2) What are the active chemotherapeutic drugs for which efficacy has been shown? 3) Which are the most effective platinum-based regimens? 4) Which is the indicated dosage of cisplatin? 5) Can carboplatin be substituted for cisplatin? 6) Which is the optimal number of cycles to be administered? 7) Can non-platinum based regimens be substituted for platinum based chemotherapy as first-line treatment? 8) Is there an indication for sequential chemotherapy? 9) What is the efficacy of salvage chemotherapy and which drugs should be used in that indication? 10) What is the place of targeted therapies? 11) What is the place of chemotherapy in the management of a patient with brain metastases? 12) Which specific drugs can be used for the patient with bone metastases?

These questions have been extensively discussed during a meeting organised in April 2006 in Brussels in Belgium. The present consensus has been definitively approved by the Group in a final meeting in Ostende, in October 2006.

METHODOLOGY

Guidelines were established on the basis of the various data published in the literature: 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 with the use of the AGREE instrument [3;4], allowing elimination of the worst ones and use of the best available ones for the establishment of our own guidelines. The following guidelines were selected: ASCO (American Society of Clinical Oncology) [5;6], BTS (British Thoracic Society) [7], Cancer Care Ontario Practice Guidelines [8], Royal College of Radiologists [9], American College of Chest Physicians (ACCP) [10] and FNCLCC (Fıdıration Nationale des Centres de Lutte contre le Cancer) [11]. Selection was based on the assessment of the literature previously performed by the ACCP [12] and it was completed by the analysis using the AGREE instrument of other guidelines that had not been taken into consideration by the ACCP. This approach allowed adding to the list the guidelines of FNCLCC and ACCP.

QUESTION 1: WHAT BENEFITS CAN BE EXPECTED FROM CHEMOTHERAPY AND WHAT ARE THE TREATMENT OBJECTIVES?

Randomised trials have shown benefits in terms of palliation, improvement of survival, symptom control, quality of live and costs. Table 1 summarises the twelve trials that assessed the effect of combination chemotherapy (cisplatin-based in all but one) versus supportive care alone [13-25]. One study

TABLE 1. Randomised trials assessing combination chemotherapy plus supportive care versus supportive care alone in advanced NSCLC.

Reference	Chemotherapy regimen	Treatment		Control		p
		n pts (% St IV)	MS (wk)	n pts (% St IV)	MS (wk)	
Cormier, 1982 [13]	MTX-ADR-CPA-CCNU	20 (50)	30	19 (47)	8	S
Rapp, 1988 [14]	I. CDDP-ADR-CPA II. CDDP-VDS	43 (86) 44 (82)	25 33	50 (90)	17	S
Ganz, 1989 [15]	CDDP-VBL	31 (100)	13	32 (100)	20	NS
Woods, 1990 [16]	CDDP-VDS	97 (74)	27	91 (57)	17	NS
Kaasa, 1991 [17]	CDDP-VP16	44 (100)	36	43 (100)	24	NS
Quoix, 1991 [18]	CDDP-VDS	24 (100)	28	22 (100)	10	S
Cellerino, 1991 [19]	CPA-epirubicine-CDDP ~ MTX-VP16-CCNU	62 (60)	34	61 (57)	21	NS
Leung, 1992 [20]	CDDP-VP16+ radiotherapy	42 (0)	50	62 (0)	35	S
Cartei, 1993 [21]	CDDP-CPA-MMC	52 (100)	36	50 (100)	17	S
Helsing, 1998 [22]	Carboplatine + VP16	22 (91)	29	26 (88)	11	S
Thongprasert, 1999 [23]	I. CDDP-epirubicine-Ifo II. CDDP- MMC- VBL	96 (?) 93 (?)	25 35	98 (?)	18	S
Cullen, 1999 [24]	MMC-Ifo-CDDP	165 (?)	29	177 (?)	21	S
Spiro, 2004 [25]	cisplatin-based (MMC-Ifo-CDDP, MMC-VDS-CDDP, CDDP-VDS, CDDP-VNR)	364 (38)	32	361 (39)	23	S

MTX: methotrexate; ADR: adriamycine; CPA: cyclophosphamide; CDDP: cisplatin; VDS: vindısine; VBL: vinblastine; MMC: mitomycin C; Ifo: ifosfamide; VNR: vinorelbine; St: stage: S: significant; NS: non significant; MS: median survival; wk: week

included only patients with stage III NSCLC [20). Two thirds of the trials showed statistically significant improvement of survival. In addition, four trials (table 2) have compared single agent chemotherapy, using one of the newer drugs with best supportive care alone [26-29]. All but one [28] showed a significant survival improvement with chemotherapy.

Five meta-analyses [30-34], published in the nineties and including one performed with individual patients data [33], have confirmed a modest but significant effect with chemotherapy in terms of survival (Ttable 3). Symptoms control has been also demonstrated as summarised in the ACCP guidelines [35], with a high rate of improvement for cough, haemoptysis, pain, dyspnoea, weight less, anorexia and malaise. Quality of life has been assessed in 8 trials, with significant improvement in all but one (table 4). Finally, in term of costs, Canadian authors have shown, in the NCI-C trial [14], a reduced cost when chemotherapy is prescribed compared with supportive care alone [36].

The published guidelines recommend treatment with chemotherapy. More specifically, the Royal College of Radiologists recommends cisplatin-based combinations in patients with performance status (PS) 0-2 but in the context of a clinical trial; the FNCLCC recommends cisplatin-based chemotherapy for patients with PS 0-1 [37]; the Cancer Care Ontario Program recommends cisplatin-based chemotherapy after a full discussion of benefit limitations and toxicity [8]; ASCO recommends two-drug combination regimens in patients with good PS (0, 1 and possibly 2) [6]; ACCP recommends platinum-based chemotherapy regimens for patients with PS 0, 1 and possibly 2 [35].

ELCWP GUIDELINES:

Chemotherapy is recommended in patients with good PS. Therapeutic objectives are survival and quality of life improvement and symptom control. Cisplatin-based chemotherapy with one of the regimens shown to be effective should be preferred. Carboplatin may be substituted for cisplatin if medical contraindications do exist. Single agent chemotherapy with a drug shown to be effective compared with supportive care, may be considered in patients with poor PS, and the choice among the active ones depends on the medical condition of the patient.

TABLE 2. Randomised trials assessing single new drug chemotherapy plus supportive care versus supportive care alone in advanced NSCLC

Reference	Treatment arm	n pts (% stage IV)	OR	Survival		
				MS	1 yr	p
Italian Elderly, 1999 [26]	1. VNR 2. -	76 (74) 78 (72)	20% -	28 w 21w	32% 14%	0.03
Ranson, 2000 [27]	1. PAC 2. -	79 (51) 78 (54)	16% -	6.8 m 4.8 m		0.037
Anderson, 2000 [28]	1. GEM 2. -	150 (41) 150 (39)	18% -	5.7 m 5.9 m	25% 22%	0.84
Roszkowski, 2000 [29]	1. DOC 2. -	137 (44) 70 (53)	13% -	6 m 5.7 m	25% 16%	0.026

VNR: vinorelbine; PAC: paclitaxel; GEM: gemcitabine; DOC: docetaxel; MS: median survival; w: week; m: month;yr: year; OR: objective response; pts: patients.

TABLE 3. Meta-analyses assessing the effect of combination chemotherapy versus supportive care in advanced NSCLC

Reference	Methodology	Outcome criteria	Trials number	Patients number	Result
Souquet, 1993 [30]	IMA	Survival at 3, 6, 9, 12 et 18 months	7	706	S
Grilli, 1993 [31]	IMA	Mortality risk	6	635	S
Marino, 1994 [32]	MALSR	Mortality risk	8	712	S
Collaborative Group, 1995 [33]	IDMA	Overall survival	11	2334	S
Sculier, 1999 [34]	MALSR	Mortality risk	6	557	S

IMA: isolated meta-analysis of the literature; MADLSR: meta-analysis with systematic review of the literature; IDMA: meta-analysis based on individual patients data; S: significant

TABLE 4. Assessment of the effect of chemotherapy on quality of life in the trials comparing chemotherapy with supportive care alone in advanced NSCLC.

Reference	Chemotherapy regimen	survival	QOL
Rapp, 1988 [14]	I. CDDP-ADR-CPA II. CDDP-VDS	S	S
Elderly Group, 1999 [26]	vinorelbine	S	S
Thongprasert, 1999 [23]	I. CDDP-epirubicine-Ifo II. CDDP- MMC- VBL	S	S
Cullen, 1999 [24]	MMC-Ifo-CDDP	S	S
Spiro, 2004 [25]	cisplatin-based (MMC-Ifo-CDDP, MMC-VDS-CDDP, CDDP-VDS, CDDP-VNR)	S	NS
Ranson, 2000 [27]	Paclitaxel	S	S
Anderson, 2000 [28]	Gemcitabine	NS	S
Roszkowski 2000 [29]	Docetaxel	S	S

ADR: adriamycine; CPA: cyclophosphamide; CDDP: cisplatin; VDS: vindesine; VBL: vinblastine; MMC: mitomycin C; Ifo: ifosfamide; VNR: vinorelbine; S: significant; NS: non significant; QOL: quality of life

QUESTION 2: WHAT ARE THE ACTIVE CHEMOTHERAPEUTIC DRUGS FOR WHICH EFFICACY HAS BEEN SHOWN?

The drugs used in the published trials can be divided in three groups: inactive (also called first-generation), old (second-generation) and new (or modern or third-generation) ones. The second-generation group of drugs has been the topic of a meta-analysis performed by our Group [38]. They include cisplatin, ifosfamide, mitomycin C, vindesine, vinblastine. Each of these drugs is able to significantly improve the response rate of the disease. The third-generation of active drugs has also been the subject of a systematic review performed by our Group [39]. They include gemcitabine, paclitaxel, docetaxel and vinorelbine, all available in Europe. In the randomised trials summarised in table 2, all these drugs, excepting gemcitabine, have been shown to improve survival in comparison to supportive care alone.

ELCWP GUIDELINES:

Chemotherapy regimens should include available active drugs. Old active (second-generation) drugs are cisplatin, ifosfamide, mitomycin C, vindesine and vinblastine. New active (third-generation) drugs are gemcitabine, paclitaxel, docetaxel and vinorelbine.

QUESTION 3: WHICH ARE THE MOST EFFECTIVE PLATINUM-BASED REGIMENS FOR FIRST LINE CHEMOTHERAPY ?

Many cisplatin-based regimens are commonly used, combining cisplatin with old drugs such as vindesine, mitomycin C and/or ifosfamide or new drugs such as gemcitabine, docetaxel, paclitaxel or vinorelbine. Our recommendation is based on the following data. In their guidelines, the Ontario Program [8] and the FNCLCC [37] recommend cisplatin-containing chemotherapy, without further precision of the drug(s) to be combined. For the ACCP, chemotherapy should be platinum-based with a new single agent [35]. For ASCO, it should be a two-drug combination regimen [6]; non-platinum containing chemotherapy may be used as an alternative to platinum-based regimen. In patients with poor performance status, ASCO recommends single-agent chemotherapy.

Two types of meta-analyses are available [40]. In the first type (table 5), the trials are compared according to the number of drugs in the regimen. Polychemotherapy is associated with better results than single agent treatment [41;42]. Two-drugs regimens are superior to one-drug regimen, both in terms of response and survival; three-drugs combinations are better to two-drugs only in terms of response [43]. In the second type (table 6), the role of specific drugs is analysed.

TABLE 5. Meta-analyses assessing the number of drugs needed in chemotherapy regimens for advanced NSCLC

Reference	Methodology	Outcome criteria	Trials number	Patients number	Result
Single agent versus polychemotherapy					
Marino, 1995 [41]	MALSR	Mortality risk	9	1493	S
Lilenbaum, 1998 [42]	IMA	Survival at 6 & 12 months	25	5156	S
One versus two drugs					
Delbaldo, 2004 [43]	IMA	Median survival	30	6022	S
Two versus three drugs					
Delbaldo, 2004 [43]	IMA	Median survival	30	4550	NS

IMA: isolated meta-analysis of the literature; MADLSR: meta-analysis with systematic review of the literature; IDMA: meta-analysis based on individual patients data; S: significant; NS: non significant

Addition of a drug to a platinum derivative is beneficial in terms of survival [44) but not the addition of mitomycin-C to a basic chemotherapy regimen [45]. Gemcitabine appears to be associated with better outcome in a meta-analysis of the literature but with much heterogeneity among the aggregated trials [46]. The combination of cisplatin with docetaxel does not appear to result in better survival in comparison to other cisplatin-based regimens [47]. In practice guidelines about the use of taxanes, in 2005, the Canadians recommend paclitaxel or docetaxel plus cisplatin as one of a number of chemotherapy options in patients with good performance status [48].

There are very few randomised trials having directly comparing cisplatin-based regimens combining new versus old drugs. Practically, cisplatin plus gemcitabine was better than cisplatin + ifosfamide + mitomycin-C in terms only of response but not of survival [49]. Cisplatin + vinorelbine was not superior to cisplatin + vindesine + mitomycin-C [50]. Cisplatin + carboplatin + gemcitabine was not better than the old combination with ifosfamide [51]. A Japanese trial compared cisplatin-irinotecan to cisplatin-vindesine, without finding a difference [52]. In another Japanese study, cisplatin plus docetaxel was shown to be better than cisplatin plus vindesine for both responses and survival [53] while a British trial, using carboplatin + docetaxel, failed to show better outcome than with the old combination MVP or MIP [54]. It should be noted that, in the early nineties, an Italian trial had shown survival advantage with these two latter regimens in comparison to the cisplatin plus etoposide combination [55].

ELCWP GUIDELINES:

Chemotherapeutic regimens should include cisplatin with at least one other active drug. If the other drug is a new one, there is no evidence for the addition of a third agent outside the context of a clinical trial. There is also no evidence that combinations with new drugs are superior to those with old drugs in terms of survival. Cost of the treatment including supportive care and complications management has to be taken into consideration in the choice of the regimen.

QUESTION 4: WHICH IS THE INDICATED DOSAGE OF CISPLATIN?

This question has not been addressed in available guidelines. There are five randomised trials on that question (table 7), all performed with old drugs [56-60]. None was able to report a significant advantage in favour of high dosages of cisplatin (100-120 mg/m^2) in comparison to lower dosages (50-60 mg/m^2). In fact, the use of high dose cisplatin is based on the observation of Gralla [56] that responders to cisplatin plus vindesine survived longer when 120 mg/m2 of cisplatin was administered instead of 60 mg/m2. This difference was observed in a very small group of patients (35 patients) and our Group was unable to replicate the results in a much higher number of patients [57]. High-dosage of cisplatin has the disadvantage of significantly higher renal, auditory and neurologic toxicities [61].

ELCWP GUIDELINES:

There is no demonstration that high doses of cisplatin (100-120 mg/m^2) provide better results than standard lower doses (50-60 mg/m^2) in terms of survival. Standard doses are associated with reduced toxicity and are thus recommended.

QUESTION 5: CAN CARBOPLATIN BE SUBSTITUTED FOR CISPLATIN?

The FNCLCC guidelines [37] and the Cancer Care Ontario Program recommend cisplatin-based chemotherapy while the American Societies ACCP [35] and ASCO [6] propose platinum-based chemotherapy, using interchangeably cisplatin and carboplatin.

The level of evidence is based on ten published randomised trials [62-71] summarised in table 8 and one meta-analysis of the literature [72]. In randomised trials, the trend is in favour of cisplatin, both in terms of response and survival. The meta-analysis confirms this impression; the results are statistically significant in favour of cisplatin if the analysis is restricted to the regimens using new drugs combined with platinum derivatives.

TABLE 6. Meta-analyses assessing the role of particular drugs for chemotherapy in advanced NSCLC.

Reference	Methodology	Outcome	N trials	N patients	Result
		Addition of a drug to a platinum derivative			
Hotta, 2004 [44]	MALSR	survival	8	2374	S
		Addition of mitomycin to a basic chemotherapy regimen			
Sculier, 2001 [130]	SRL with MA	Overall survival	10	1769	NS
		Role of chemotherapy with gemcitabine in comparison to other drugs			
Le Chevalier, 2005 [46]	IMA	Survival	13	4556	S
		Cisplatin + docetaxel versus other associations with cisplatin			
Sanchez Lerma, 2004 [47]	IMA	Overall survival	3	1980	NS

IMA: isolated meta-analysis of the literature; MADLSR: meta-analysis with systematic review of the literature; S: significant; NS: non significant

TABLE 7. Randomised trials assessing the role of the dosage of cisplatin

Reference	Regimen	n	(st IV)	% OR	p	MST	p
Gralla, 1981	I. CDDP (120 mg/m2) +VDS	41		40	NS		NS
	II. CDDP (60 mg/m2) +VDS	40		46			
Klastersky, 1986	CDDP-VP16				NS		NS
	I. 120 mg/m2	116	(63)	29		28 w	
	II. 60 mg/m2	125	(76)	25		33 w	
Shinkai, 1986	I. CDDP (120 mg/m2) +VDS	24	(19)	39	NS	9 m	
	II. CDDP (80 mg/m2) +VDS	21	(16)	33		10.8 m	
Gandara, 1993	CDDP				NS		NS
	I. 2 x 100 mg/m2	108	(108)	14		5.3 m	
	II. 2 x 50 mg/m2	105	(105)	12		6.9 m	
Sculier, 2000	Ifo – MMC				NS		NS
	I.CDDP 50 mg/m^2	147	(143)	27		28 w	
	II. CDDP 60 mg/m^2 + CBDCA (200 mg/m^2)	150	(145)	33		32 w	

CDDP: cisplatin; CBDCA: carboplatine; VDS: vindesine; MMC: mitomycin C; Ifo: ifosfamide; NS: non significant; st: stage; OR: objective response; MST: median survival time; w: week; m: month

TABLE 8. Randomised trials comparing cisplatin-based with carboplatin-based regimens in advanced NSLC

Reference	Chemotherapy	n	% OR	p	MST	p
Klastersky, 1990 [62]	I. CDDP (120 mg/m2) + VP16	114	27	0.07	30 w	NS
	II. CBDCA (325 mg/m2)+VP1 6	114	16		27 w	
Comella, 1994 [63]	I. CDDP (60 mg/m2) + VP16+ epir.	28	62	NS	?	
	II. CBDCA (300 mg/m2) + VP16 + epir.	30	59		?	
Jelic, 2001 [64]	I. CDDP (120 mg/m^2) + MMC + VDS	112	36	NS		0.008
	II. CBDCA (500 mg/m^2) + MMC + VDS	107	30			
Schiller, 2002 [65]	I.CDDP (75 mg/m^2) + Paclitaxel (135 mg/m^2)	303	21	NS	7.8 m	NS
	II.Carbo (AUC 6) + Paclitaxel (225 mg/m^2)	299	17		8.1 m	
Rosell, 2002 [66]	I.CDDP (80 mg/m^2) + Paclitaxel (200 mg/m^2)	309	27	NS	9.8 m	0.02
	II. CBDCA (AUC 6) + Paclitaxel (200 mg/m^2)	309	24		8.2 m	
Mazzanti, 2003 [67]	I. CDDP (80 mg/m^2) + gemcitabine	62	42	NS	10 m	NS
	II. Carboplatine (AUC 5) + gemcitabine	58	31		10.8 m	
Fossella, 2003 [68]	I. Docetaxel + CDDP (75)	408	32	S	11.3 m	0.044
	II. Docetaxel + Carboplatine (AUC 6)	404	24		9.4 m	
	III. CDDP (100) + VNR	404	24,5		10.1 m	
Zatloukal, 2003 [69]	I. CDDP (80) + gemci	87	41	0.09	8.7 m	0.9
	II Carboplatin (AUC 5) + gemci	89	29		8 m	
Paccagnella, 2004 [70]	I. CDDP (100) + MMC + VBL	75	38	NS	7.2 m	0.19
	II. Carboplatine (300) + MMC + VBL	78	43		10 m	
Chen, 2006 [71]	I. Paclitaxel (160) + CDDP (60)	41	30	NS	10.5 m	
	II. Paclitaxel (160) + Carbo (AUC 6)	40	40		10.3 m	

CDDP: cisplatin; CBDCA: carboplatine; VDS: vindesine; VBL: vinblastine; MMC: mitomycin C; Ifo: ifosfamide; VNR: vinorelbine; epir: epirubicine ; NS: non significant; st: stage; OR: objective response; MST: median survival time; w: week; m: month

ELCWP GUIDELINES:

Cisplatin should be preferred to carboplatin because of a better effect on survival. Carboplatin or a non-platinum based regimenmay be prescribed if the patient is unable or unwilling to take cisplatin.

QUESTION 6: WHICH IS THE OPTIMAL NUMBER OF CYCLES TO BE ADMINISTERED?

ACCP recommends short treatment with 3 to 4 cycles and ASCO no more than 6 cycles, maximum of 4 if no response is observed [6]. Other scientific societies do not make recommendations about chemotherapy duration.

In fact, the level of evidence is poor, based on a limited number of randomised trials shown in table 9 [73-76]. Two studies compared 3 with 6 cycles [73;77] and another 4 cycles with treatment until disease progression [74]. The last two trials compared, after induction chemotherapy, maintenance treatment using paclitaxel [75] or vinorelbine [76] versus observation. In none, prolongation of chemotherapy demonstrated an advantage.

ELCWP GUIDELINES:

The optimal duration of chemotherapy in advanced NSCLC, is poorly defined. A minimum of 4 to 6 cycles is proposed in responding patients. Prolongation with single drug appears ineffective in terms of survival. The attitude of continuing treatment until best response merits further assessment.

QUESTION 7: CAN NON-PLATINUM BASED REGIMENS BE SUBSTITUTED FOR PLATINUMBASED CHEMOTHERAPYAS FIRST LINE TREATMENT?

ASCO is the only scientific society recommending non-platinum regimens as an alternative for platinum-based chemotherapy as first-line treatment of patients with advanced NSCLC [6]. For all other societies, chemotherapy in that indication should be platinum-based.

Randomised published trials [51;78-95] on the topic are summarised in table 10. In terms of survival, there is no statistically significant difference between the 2 types of treatment in all but one trial. Barlesi and Pujol [96] have performed in 2005 a systematic review of the phase III trials available in the literature. They concluded that the approach is still debatable when doublet-regimens with new drugs are considered. They did not report a meta-analysis. D'Addario et al [97] have performed a meta-analysis of the published literature. When all trials were considered (irrespectively of using old or new drugs), there was a significant advantage both for response rate and 1-year survival in favour of platinum-based treatment. The increase in 1-year survival was 5%. When the analysis was restricted to combination regimens with new drugs, there was no significant difference in survival but response rate was significantly improved with platinum-based treatment.

ELCWP GUIDELINES:

Non-platinum-based regimens as first-line treatment for

TABLE 9. Randomised trials assessing the duration of chemotherapy in advanced NSCLC.

Reference	Regimen	n	(st IV)	% OR	p	MST	p
Smith, 2001 [73]	CDDP (50 mg/m^2) + MMC + VBL				NS		NS
	I. 3 cycles	155	(72)	31		6 m	
	II. 6 cycles	153	(81)	32		7 m	
Socinski, 2002 [74]	Carbo (AUC 6) + paclitaxel (200)				NS		NS
	I. 4 cycles	114	(100)	22		6.6 m	
	II until progression	116	(100)	24		8.5 m	
Belani, 2003 [131]	Carbo + paclitaxel 4 cycles: CR/PR/NC:						NS
	I. paclitaxel 70 mg/m^2/wk 3 wk/4	66	72%			75 w	
	II. observation	65	78%			60 w	
Westeel, 2005 [76]	Response to MMC + Ifo + CDDP	573					NS
	I. -	90	53%			12.3 m	
	II VNR 6 months	91	43%			12.3 m	
Von Plessen, 2006 [77]	Carbo + vinorelbine						
	I. 3 cycles	150	(113)	NA		28 w	NS
	II. 6 cycles	147	(113)	NA		32 w	

CDDP: cisplatin; Carbo: carboplatine; VBL: vinblastine; MMC: mitomycin C; Ifo: ifosfamide; NS: non significant; st: stage; OR: objective response; MST: median survival time; w: week; m: month; NA: not available

TABLE 10. Randomised trials testing platinum-based regimens versus non-platinum-based regimens as primary chemotherapy for advanced NSCLC.

Reference	Chemotherapy (dosage)	n	(st IV)	% OR	p	MS	p
Georgoulias, 2001 [78]	I. CDDP (80 mg/m²)+docetaxel (100 mg/m²)	205	(129)	35		10 m	
	II. Gemci + docetaxel (100 mg/m²)	201	(130)	33	NS	9.5 m	NS
Sculier, 2002 [51]	I.CDDP (50) + CBDCA (200) + Ifo	94	all	23		24 wk	
	II.CDDP(50) + CBDCA (200) +Gemci	92		29	NS	34 wk	NS
	III.Ifo + gemcitabine	94		25		30 wk	
Kosmidis, 2002 [79]	I. Paclitaxel (200 mg/m²) + Carbo (AUC 6)	252	(158)	28		10.4 m	
	II. Paclitaxel (200 mg/m²) + gemcitabine	257	(148)	35	0.12	9.8 m	0.32
Greco, 2002 [80]	I. CBDCA (AUC 5)+paclitaxel (200)+ gemci	71	(51)	37		9.2 m	
	II. CBDCA (AUC 6)+paclitaxel (200)+ VNR	65	(51)	45	NS	8.6 m	NS
	III. paclitaxel (200)+ gemci	64	(53)	32		8.7 m	
	IV. Gemci + VNR	67	(49)	33		10.7 m	
Chen, 2002 [81]	I. Carboplatine (AUC 7) + paclitaxel (175)	45		40		14.1 m	
	II. paclitaxel (175) + gemci	45		40		12.6 m	
Gebbia, 2003 [82]	I. CDDP + gemcitabine	138	(73)	34		8.2 m	
	II. CDDP + vinorelbine	140	(75)	44	0.007	9.0 m	NS
	III. Ifo + gemcitabine then CDDP + VNR	60	(33)	19			
	IV. CDDP + VNR then Ifo + gemcitabine	60	(31)	31			
Gridelli, 2003 [83]	I. CDDP (80) + VNR	126	80%				
	II. CDDP (80) + gemcitabine	126	81%	30	NS	38 wk	0.08
	III. VNR + gemcitabine	251	80%	25		32 wk	
Alberola, 2003 [84]	I. CDDP (100) + gemcitabine	182	77 %	42		9.3 m	
	II. CDDP (100) + gemcitabine + VNR	188	79 %	41	S	8.2 m	NS
	III. gemci + VNR x 3 then Ifo + VNR x 3	187	81 %	27		8.1 m	
Smit, 2003 [85]	I. paclitaxel (175) + CDDP (80)	159	(130)	32		8.1 m	
	II. CDDP (80) + gemci	160	(126)	37	NS	8.9 m	NS
	III. paclitaxel (175) + gemci	161	(136)	28		6.7 m	
Wachters, 2004 [86]	I. CDDP + gemcitabine	119	57%	46%	NS	43 wk	0.14
	II. Epirubicine + gemcitabine	121	57%	36%		36 wk	
Yamamoto, 2004 [87]	I. CDDP (80) + docetaxel (60)	51	(40)	37 %	NS	50 wk	NS
	II. Irinotecan + docetaxel (60)	57	(43)	32 %		46wk	
Laack, 2004 [88]	I. CDDP (75 J2) + gemci + VNR	144	(126)	28 %	0.004	32 wk	0.73
	II. gemci + VNR	143	(125)	13 %		36 wk	
Stathopoulos, 2004 [89]	I. Paclitaxel (135) + vinorelbine	175	47%	43 %	NS	10 m	NS
	II. Paclitaxel (175) + carboplatine (AUC 6)	185	49%	46 %		11 m	
Lilenbaum, 2005 [90]	I. gemci + VNR	82	82%	14,6 %		7.8 m	
	II. Paclitaxel + carboplatine	83	81%	16,9%		8.6m	
Chen, 2005 [91]	I. VNR (20 d1,8,15) + gemci (800 d1,8,15)	43	77%	23 %	0.02	9.5 m	NS
	II. Idem + CDDP (60 d15)	43	81%	46 %		13.1 m	
Pujol, 2005 [92]	I. Gemcitabine + docıtaxel (85)	155	79 %	31 %	NS	11.1 m	NS
	II. CDDP (100) + vinorelbine	156	86 %	36 %		9.6 m	
Georgoulias, 2005 [93]	I. Vinorelbine (30 d1 & 8) + CDDP (80 d8)	204	64%	39 %	0.053	8.6 m	NS
	II. Gemcitabine (1 d1 & 8) + docetaxel (80 d8)	209	62%	30 %		9.0 m	
Tan, 2005 [132]	I. Gemcitabine + vinorelbine	157	80%	28 %	0.15	11.5 m	0.01
	II. Carboplatine (AUC 5) + vinorelbine	159	90%	21 %		8.5 m	
Katagami, 2006 [95]	I. Docetaxel (60) + cisplatine (80)	68	73%	23%	NS	11.4 m	NS
	II. Docetaxel (60) + gemcitabine	63	75%	27%		13.7 m	

CDDP: cisplatin; CBDCA: carboplatine; Ifo: ifosfamide; VNR: vinorelbine; St: stage: S: significant; NS: non significant; OR: objective response; MST: median survival time; MS: median survival; wk: week; d: day

advanced NSCLC, may be used in cases where platinum-based chemotherapy is contra-indicated. For all other patients, they should be used only in the context of clinical trials.

QUESTION 8: IS THERE AN INDICATION FOR SEQUENTIAL CHEMOTHERAPY?

There is only one randomised phase II trial published on the topic [98]. The ELCWP has completed a large phase III trial where patients without disease progression after 3 courses of cisplatin-based chemotherapy were randomised between further platinum-based chemotherapy or paclitaxel with crossover at the time of progression. There was no difference in survival between the two approaches, the trend being in favour of the non-sequential approach.

ELCWP GUIDELINES:

There is no indication for sequential chemotherapy with taxanes (or other drugs) in the management of advanced NSCLC.

QUESTION 9: WHAT IS THE EFFICACY OF SALVAGE CHEMOTHERAPY AND WHICH DRUGS SHOULD BE USED IN THAT INDICATION?

Second-line chemotherapy is recommended in the guidelines of ACCP and ASCO. According to ACCP, it should be offered in patients with good PS [35]. According to ASCO, it should be consisted of docetaxel followed by gefitinib [6].

There is only one randomised trial having compared second-line chemotherapy with supportive care alone in advanced NSCLC. Survival was significantly improved in the chemotherapy arm [99]. Other trials (table 11) have compared docetaxel to vinorelbine or ifosfamide [100], paclitaxel [101], pemetrexed [102] or oral topotecan [103]. None of the alternative approaches was shown to be better than docetaxel in terms of survival or response rate. Some improvement was reported with pemetrexed in terms of tolerance. Implementation studies have reported results similar to randomised trials when docetaxel was used in routine application [104;105]. Weekly administration of docetaxel has not been shown to be better [106-110] than three weekly treatment (table 12). A dosage of 75 mg/m^2 appears to be better tolerated than 100 mg/m^2 [111].

A systematic review of the literature concluded that second-line chemotherapy produces a small but significant survival benefit [112].

ELCWP GUIDELINES:

Second-line chemotherapy should be offered to patients with good performance status, failing platinum-based first-line chemotherapy. Evidence is in favour of docetaxel (if not already administered as first-line treatment) given on a 3-weekly schedule at a dosage of 75 mg/m^2. Additional controlled data are needed before substituting pemetrexed for docetaxel.

QUESTION 10: WHAT IS THE PLACE OF TARGETED THERAPIES?

EGF-R tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib, have been the subject of intensive clinical research during the last few years. Erlotinib is the first targeted drug commercially available in Europe for the management of NSCLC.

Results were disappointing when TKIs were used as first-line therapy in association with chemotherapy. Three large randomised trials were conducted, two with gefitinib by Giaccone and Herbst [113;114] and one with erlotinib by Herbst [115]. When they were also used as salvage therapy after chemotherapy failure (table 13), TKIs were shown to be superior to placebo, with a statistically significant survival advantage in the erlotinib trial [116]. The survival advantage was less

TABLE 11. Randomised trials testing salvage chemotherapy for NSCLC

Reference	Chemotherapy	n	% OR	p	MST	p
Shepherd, 2000 [99]	1. DOC	104	6		7 m	0.047
	2. BSC	100	-		4.6 m	
Fossella, 2000 [100]	1. DOC 100 mg/m^2	60	11			
	2. DOC 75 mg/m^2	59	7	0.002		0.025
	3. VNR ou Ifo	60	1			
Esteban, 2003 [101]	1. DOC26 mg/m^2/wk	35	3		105 d	NS
	2. Paclitaxel 80 mg/m^2/wk	36	14	NS	184 d	
Hanna, 2004 [102]	1. Pemtrexed 500 mg/m^2	283	9	NS	8.3 m	NS
	2. DOC 75 mg/m^2	288	8		7.9 m	
Ramlau, 2006 [103]	I. Topotecan oral 2,3 mg/m^2 d1-5	414	5	NS	28 wk	0.057
	II. DOC 75 mg/m^2/3 wk	415	5		31 wk	

DOC: docetaxel; Ifo: ifosfamide; VNR: vinorelbine; St: stage; NS: non significant; OR: objective response; MST: median survival time; MS: median survival; wk: week ; d: day; m: month

TABLE 12. Randomised trials testing weekly versus 3 weekly docetaxel as salvage chemotherapy for advanced NSCLC

Reference	Chemotherapy	n	% OR	p	MST	p
Gervais, 2005 [106]	1. Docetaxel 75 mg/m²/3 wk	62	4.8		5.8 m	
	2. Docetaxel 40 mg/m²/ wk	63	3.2		5.6 m	
Gridelli, 2004 [107]	1. Docetaxel 75 mg/m²/3 wk	110		NS	29 wk	NS
	2. Docetaxel 33.3 mg/m²/wk	110			25 wk	
Schuette, 2005 [108]	I. Docetaxel 75 mg/m²/3 wk	103	12.6	NS	6.3 m	0.07
	II. Docetaxel 35 mg/m²/wk	105	10.5		9.2 m	
Camps, 2006 [109]	I. Docetaxel 75 mg/m²/3 wk	131	9.3	NS	6.6 m	0.07
	II. Docetaxel 36 mg/m²/wk	128	4.8		5.4 m	
Chen, 2006 [110]	I. Docetaxel 35 mg/m² d1,8,15 every 4 wk	64	17.2		8.4 m	
	II. Docıtaxel 40 mg/m² d1 & 8 every 3 wk	64	10.9	NS	7.2 m	NS
	III. Docıtaxel 75 mg/m²/3 wk	33	6.1		9.5 m	

NS: non significant; OR: objective response; MST: median survival time; MS: median survival; wk: week ; d: day; m: month

evident with gefitinib [117]. Response rates were low (less than 10%) but some initial characteristics of the patients or of the disease (female gender, Asian ethnic origin, adenocarcinoma, no smoking history) were associated with significantly better response rates. Some biological characteristics of the tumour were also associated with better outcome. EGF-R-positive immunohistochemisty and EGF-R amplification detected by FISH were positively associated with response and survival in erlotinib treatment patients [118]. Mutant EGF-R was not significantly associated with response but these data are controversial due to technical problems [119;120]. For gefitinib, EGF-R gene mutation is associated with much higher response rates [121]. Recent data were presented in the last ASCO meeting (Atlanta, 2006), as shown in table 14. When TKIs were given in chemotherapy-naive patients whose tumour demonstrated EGF-R gene mutations, the response rate was very high (around 70 to 80%). A Japanese recent publication reports a rate of 75% [122]. Controlled trials are necessary to determine if TKIs could replace chemotherapy in this type of patients.

ELCWP GUIDELINES:

EGF-R tyrosine kinase inhibitors should not be used as initial treatment of patients with advanced NSCLC. Erlotinib can be used as salvage treatment in patients whose tumour shows abnormal expression of EGF-R. Target identification on the tumour merits further investigations.

QUESTION 11: WHAT IS THE PLACE OF CHEMOTHERAPY IN THE MANAGEMENT OF A PATIENT WITH BRAIN METASTASES?

Brain metastases is usually treated by non systemic treatment such as surgery, whole-brain irradiation and, more recently, stereotactic radiosurgery. In the ELCWP experience, the presence of brain metastases in stage IV NSCLC patients treated with chemotherapy, is not an adverse prognostic factor in terms of survival or response [123-125].

There is only one controlled trial published concerning timing of brain irradiation in minimally symptomatic patients. The problem was if brain irradiation has to be administered early or can be delayed while systemic chemotherapy is delivered [126]. A total of 176 patients with NSCLC and inoperable brain metastases, treated by 6 cycles of cisplatin plus vinorelbine, were randomised between early brain irradiation (during cycle 1) or delayed brain irradiation (when no response of brain metastases to chemotherapy or after chemotherapy). There was no difference between the two approaches in terms of extracranial response rate, intracranial response rate or

TABLE 13. Randomised trials assessing tyrosine kinase inhibitors as salvage treatment for NSCLC

Reference	Regimen	N	OR	p	MST	p
Sheperd, 2005 [116]	I. erlotinib 150 mg/d	488	8.9	S	6.7 m	<0.001
	II. placebo	243	1		4.7 m	
Thatcher, 2005 [117]	I. gefitinib 250 mg/d	1129	8		5.6 m	0.087
	II. placebo	563			5.1 m	

OR: objective response; MST: median survival time; MST: median survival time; d: day; m: month

TABLE 14. Effects of tyrosine kinase inhibitors (TKI) in patients with mutations of the EGFr gene: prospective trials (excepting one) presented at ASCO 2006

Author	Screened	Mutations	TKI	N pts	RR	PFS	OS
Paz-Ares (# 7020)	1047	18.7%	erlotinib	43	82% 5CR	13 m	82% (1 yr)
Okamoto (# 7073)	104	27%	gefitinib	25	75%		
Takano (# 7075) retrospective	207	41%	gefitinib	86	78%	9.2 m	20 m
Sutani (# 7076)	100	38%	gefitinib	38	78%	9.4 m	15 m
Morikawa (# 7077)	123	37%	gefitinib	46	69%	9.7 m	
Richard (# 7184)	111	17%	gefitinib or erlotinib	7	57%		

Pts: patients; RR: response rate; PFS: progression-free survival; OS: overall survival; m: month; yr: year

overall survival.

ELCWP GUIDELINES:

Minimally symptomatic patients with brain metastases should receive systemic chemotherapy. Brain irradiation can be safely delayed until the completion of chemotherapy or when no response of brain metastases to chemotherapy is documented.

QUESTION 12: WHICH SPECIFIC DRUGS CAN BE USED FOR THE PATIENT WITH BONE METASTASES?

Bone metastases can be treated when necessary, by local treatment including irradiation, surgery or cimentoplasty or by systemic chemotherapy. The question arises if the addition of bisphosphonates in the patient with NSCLC and metastatic bone lesions is a useful approach.

There is no specific trial testing bisphosphonates in NSCLC. A randomised study has been performed with zoledronic acid in patients with solid tumours [127;128]. There were significantly less skeletal-related events with zoledronic acid in comparison to placebo. In a subgroup analysis for lung cancer patients, the skeletal-related events were significantly reduced but, if hypercalcaemia was not taken into consideration, the effect was only marginal. It should be noted that late complications of bisphosphonates administration (mandibular necrosis) have been recently reported [129].

ELCWP GUIDELINES:

Bisphosphonates are a therapeutic option in patients with uncontrolled bone metastases despite adequate local treatment and systemic chemotherapy. The risk of mandibular necrosis has to be taken in consideration.

CONCLUSIONS

The ELCWP guidelines can be summarised as follows :

1. Chemotherapy is recommended in patients with good PS. Treatment objectives are survival, quality of life and symptom control improvement.
2. Chemotherapy regimens should include active drugs. Active old (second-generation) drugs are cisplatin, ifosfamide, mitomycin C, vindesine and vinblastine. Active new (third-generation) drugs are gemcitabine, paclitaxel, docetaxel and vinorelbine.
3. Cisplatin-based chemotherapy with one of the effective regimens should be used. If the second drug is a new one, there is no evidence for the addition of a third agent outside the context of a clinical trial. There is also no evidence that combinations with new drugs are superior to those with old drugs in term of survival.
4. There is no conclusive evidence that high doses of cisplatin (100-120 mg/m^2) provide better results than standard lower doses (50-60 mg/m^2) in terms of survival. Standard doses are associated with reduced toxicity and are thus recommended.
5. Cisplatin should be the preferred drug compared to carboplatin because of a better survival outcome. Carboplatin may be prescribed if the patient is unable or unwilling to receive cisplatin.
6. The optimal duration of chemotherapy is poorly documented in advanced NSCLC. A minimum of 4 to 6 cycles is advised in responding patients. Prolongation of treatment by single drug appears ineffective in term of survival.
7. Non-platinum-based regimens are indicated as first-line treatment for advanced NSCLC in patients for whom platinum-based chemotherapy is contra-indicated. Single drug chemotherapy may be considered in patients with poor PS. The choice of the active drugs depends on the patient's medical condition.
8. There is no indication for sequential chemotherapy with taxanes (or other drugs) in the management of advanced NSCLC.
9. Second-line chemotherapy should be offered in patients with good performance status, failing on or after platinum-based first-line chemotherapy. Evidence is in favour

of docetaxel (if not administered as first-line treatment) given on a 3-weekly schedule at a dosage of 75 mg/m^2.

10. EGFR tyrosine kinase inhibitors should not be used as initial treatment of patients with advanced NSCLC. Erlotinib can be used as salvage treatment in patients whose tumour shows abnormal expression of EGFR.
11. Minimally symptomatic patients with brain metastases should receive systemic chemotherapy. Brain irradiation can be safely delayed until the completion of chemotherapy or be given when no response of brain metastases to chemotherapy is documented.
12. Bisphosphonates is a therapeutic option in patients with uncontrolled bone metastases despite adequate local treatment and systemic chemotherapy. The risk of mandibular necrosis has to be taken in consideration.
13. Cost of the treatment including supportive care and complications management has to be taken into consideration in the choice of the regimen.

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