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Long-term Survival After Chemotherapy Containing Platinum Derivatives in Patients With Advanced Unresectable Non-small Cell Lung Cancer

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The study set out to determine the rate of long-term survivors (LTS) in patients treated with platinum-containing chemotherapy for advanced non-small cell lung cancer (NSCLC), to identify prognostic factors predicting long-term survival (≥2 years) and to report the LTS natural history. Eligible patients with advanced NSCLC treated by chemotherapy in one of seven trials conducted by the European Lung Cancer Working Party from December 1980 to August 1991 were included. All patients received cisplatin and/or carboplatin. Of these, 1052 patients were eligible and 24 variables were analysed as potential prognostic factors. Actuarial 2-year and 5-year survival rates were, respectively, 7.4 and 1.8%. All patients surviving for ≥5 years had limited disease and were treated by complementary chest irradiation and/or surgery. Univariate prognostic factor analysis for LTS identified as significant no major weight loss, limited disease, no liver metastases, normal white blood cells and neutrophils and normal lactic dehydrogenase levels. By multivariate analysis, the only significant factor was limited disease. Objective response to chemotherapy was also found to be, as disease extent, a highly significant predictor for LTS. Thus, the two best prognostic factors for LTS were non-metastatic disease and response to chemotherapy.
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INTRODUCTION

NON-SMALL cell lung cancer (NSCLC) is a major cause of death by cancer. Surgery is the major curative treatment, but it cannot be performed in the majority of patients because the disease is too advanced at the time of diagnosis. Chest irradiation can be used, mainly for palliation, for locoregionally advanced disease, and chemotherapy has a controversial role in the routine management of NSCLC. Despite recent technical advances in both therapeutic modalities, no major improvement in survival has yet been achieved [1,2].

The effect of chemotherapy in patients with NSCLC is limited [3]: combination regimens induced about 30–40% objective responses (OR) in patients with non-metastatic disease (mainly stage III), and a lower rate in those with distant metastases (stage IV). Cisplatin is considered to be the drug of choice by the majority of authors [3]. The impact on survival, although often positive in randomised trials comparing chemotherapy to best supportive care, remains small [4].

Very few data are available in the literature on the long-term survival of chemotherapy-treated patients with NSCLC. In the ECOG (Eastern Cooperative Oncology Group) experience [5], overall median survival of patients with metastatic NSCLC treated by chemotherapy was 23.5 weeks, with 19% of the patients surviving for >1 year and 4% for >2 years. Pretreatment characteristics associated with longer survival were an initial performance status (PS) of 0, no bone metastases, female sex, no subcutaneous metastases, no large cell histology, <5% prior weight loss, no symptoms of shoulder or arm pain and no liver metastases. In the SWOG (South West Oncology Group) experience [6], the overall median survival was 5.1 months, with a 16% 1-year survival. Good PS, female sex, and age ≥70 years were significant independent survival predictors.

The purpose of the present study was to determine the rate of long-term survivors (LTS) in 1052 patients, treated by chemotherapy containing platinum derivatives for advanced NSCLC in consecutive trials conducted by the European Lung Cancer Working Party (ELCWP) [7–13], to identify prognostic factors predicting long-term survival (≥2 years), and to report the natural history of these LTS after chemotherapy.

PATIENTS AND METHODS

Patients and trials

The patients included in our analysis are the eligible patients with NSCLC treated by chemotherapy (followed in a few cases by radiotherapy) and registered in a clinical trial of the ELCWP from December 1980 to August 1991. These trials [7–13] are described in Table 1. They were single regimen phase II

Table 1. Chemotherapy regimen (with drug dosage in mg/m²) used in consecutive trials

Trial (Reference)	Cisplatin	Etoposide	Vindesine	Carboplatin	5-Fluorouracil	Mitomycin	Ifosamide
I (7)	60 d1	120 d3,5,7	1.5 d1,7	—	—	—	—
II (8)*	60 d1	120 d3,5,7	1.5 d1,7	—	—	—	—
III (9)	A 60 d1	120 d3,5,7	—	—	—	—	—
	B 120 d1	120 d3,5,7	—	—	—	—	—
IV (10)	A 120 d1	—	—	—	—	—	—
	B 120 d1	100 d1,2,3	—	—	—	—	—
V (11)	A 120 d1	100 d1,2,3	—	—	—	—	—
	B —	100 d1,2,3	—	325 d1	—	—	—
VI (12)	30 d1,2,3,(4)	—	3 d1	—	1000 d1,2,3,(4)	10 d1	—
VII(13)	A 120 d1						
	B 30 d2,3,	—	—	200 d1	—	—	—
	C 30 d2,3	—	—	200 d1	—	—	1500 d1,2,3

* With chest irradiation (55 Gy over 5.5 weeks) given after three courses of chemotherapy. d, day.

[7, 8, 12], randomised phase II [13] or randomised phase III [9–11] studies.

Eligibility criteria included a pathologically proven, unresectable NSCLC, with presence of an evaluable or measurable lesion in a patient with a Karnofsky performance status of at least 60. Prior chemotherapy was not allowed in trials II, IV, V and VII. Patients with both limited (LD = stage I to III) or metastatic disease (MD = stage IV) were eligible, except in trials II (only LD without pleural effusion) and VII (only MD or stage III B with pleural effusion). Age had to be <75 years, except in trial VI, where no age limit was set. There should have been no history of other malignancies, except in trials VI and VII (in trial VII, a 5-year tumour-free period was required). Brain metastases were a criterion of exclusion, except in trials VI and VII. In all trials, adequate renal, hepatic and haematological functions were required, as well as absence of a recent myocardial infarction or active cardiac or infectious diseases.

The minimal staging work-up before treatment included clinical examination, electrocardiogram, chest X-rays, chest computed tomography (CT) scan, bronchoscopy, bone scintigraphy with X-rays or CT scan of suspected areas, isotopic scan, CT scan and/or echography of liver (and possibly adrenals), isotopic scan or CT scan of the brain, laboratory studies including haematological, renal and hepatic tests. Evaluation with the same work-up was performed after two (trials I, III, VI) or three (trials II, IV, V, VII) courses of chemotherapy.

Patients were considered as assessable for response if they completed this work-up. Responses were evaluated during regular meetings of the group by at least three independent observers. Complete response (CR) was defined as the disappearance of all signs of disease, including lesions seen at bronchoscopy, for at least 4 weeks. In measurable disease, partial response (PR) consisted of a 50% or greater decrease of the sum of the products of cross measurements of individual lesions as established by two observations no less than 4 weeks apart and with no appearance of new lesions or progression of any lesion. The tumour load was estimated as the tumour area calculated by the multiplication of the longest diameter by the greatest perpendicular one. In evaluable disease, PR was defined as an estimated decrease in tumour size of 50%. Progression was considered in the case of an increase greater than 25% in one or more measurable or evaluable lesions, or of the appearance of new lesions. All other circumstances were classified as no change. Patients with early deaths due to progression of the disease before any evaluation and those with toxic deaths due to chemotherapy as well as those who discontinued treatment because of excessive toxicity were considered as assessable. More details on the trial methodology have been previously described [7–13].

We analysed, as potential prognostic factors, a total of 24 variables as shown in Table 2. All the data were prospectively collected on specific case report forms, and all the pretreatment characteristics were included in our data base.

Statistical methodology

The statistical analysis was performed using the softwares SPSS/PC [14] and BMDP [15], as well as personally written programmes. The dependent variables that were studied are the survival duration defined as the time elapsed from the date of registration until death or the date of analysis (1 August 1992), expressed in weeks, and the dichotomous variable representing the status of LTS of a patient: a patient was classified as a LTS if his/her survival duration was equal to or longer than 2 years. The influence of the pretreatment, independent variables was studied by univariate and multivariate analyses. For this purpose, we categorised all these potential prognosis variables that

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Table 2. Univariate prognostic factor analysis for long-term survival (LTS)

	Not LTS (<2 years)	LTS (≥2 years)	*P*
Number of patients	863	65	
Age			
≤60 years	41% (358)	43% (28)	
>60 years	59% (505)	57% (37)	NS
Sex			
Male	90% (780)	89% (58)	
Female	10% (83)	11% (7)	NS
Weight loss*			
≤5%	56% (429)	76% (44)	
>5%	44% (341)	24% (14)	0.004
Histological type			
Squamous cell	58% (500)	62% (40)	
Adenocarcinoma	31% (264)	28% (18)	
Other	11% (99)	11% (7)	NS
Prior therapy*			
No	87% (752)	92% (60)	
Yes	13% (109)	8% (5)	NS
Karnofsky PS			
≤70	43% (373)	32% (21)	
≥80	27% (490)	68% (44)	NS
Extent			
Stage I–III	38% (328)	58% (38)	
Stage IV	62% (535)	42% (27)	0.001
Site of metastases			
Lung	17% (133)	10% (6)	NS
Liver	22% (131)	8% (4)	0.04
Bone	35% (199)	22% (10)	NS
Adrenals	15% (82)	9% (4)	NS
Brain	8% (47)	4% (2)	NS
Skin	4% (22)	2% (1)	NS
Type of lesion*			
Evaluable	52% (445)	49% (32)	
Measurable	48% (416)	51% (33)	NS
Biological tests			
Increased WBC	43% (366)	27% (17)	0.01
Increased neutrophils	41% (338)	24% (15)	0.01
Increased platelets	29% (241)	22% (14)	NS
Decreased haemoglobinaemia	25% (212)	17% (11)	NS
Increased alkaline phosphatase	62% (492)	65% (40)	NS
Increased bilirubinaemia†	3% (25)	2% (1)	NS
Increased creatininaemia†	26% (209)	23% (15)	NS
Increased serum LDH	68% (332)	52% (21)	0.02
Hypercalcaemia	7% (38)	0	NS
Hyponatraemia	2% (11)	4% (2)	NS

NS, non-significant; PS, performance status; WBC, white blood cells; LDH, lactate dehydrogenase. Absolute number of patients in parentheses. * Some data missing. † >1 mg/dl.

are listed with their categories in Table 2. The biological values were dichotomised into normal and abnormal values, according to standard laboratory norms. For univariate analysis, we estimated the survival curves by the classical method of Kaplan and Meier, and compared these curves for a given factor by the log rank test [16]. The distributions of the LTS status were compared by χ^2 tests. The data were further fitted with a logistic regression model for LTS status [17]. The explanatory variables were selected by using a stepwise forward procedure with an enter limit fixed as a significance probability of 0.05. Confidence intervals (CI) for relative risks were calculated. All the probability significances that were calculated are two-tailed.

RESULTS

The present analysis was performed on a population of 1052 patients treated in the following trials (Table 1): 64 in trial I, 27 in trial II, 238 in trial III (114 in the first arm, 124 in the second one), 162 in trial IV (81 in each arm), 228 in trial V (114 in each arm), 181 in trial VI and 152 in trial VII (50 in each of the first two arms, 52 in the third one). Median follow-up was 270 weeks (range 53–606). At time of analysis (31 August 1992), 951 patients (90.4%) had died, 42 were (4.0%) alive and 59 (5.6%) had been lost to follow-up.

Overall median survival, actuarial 2-year and 5-year survival rates were, respectively, 29 weeks (95% CI 27–30 weeks) 7.4% (CI 5.7–9.1%) and 1.8% (CI 0.9–2.7%). Figure 1 shows the overall survival curve.

65 patients (6.2%) were LTS, including 16 still alive at the time of the analysis. Of the 1052 patients, 928 were eligible for statistical analysis requiring a follow-up of at least 2 years.

An univariate prognostic factor analysis was performed to determine pretreatment patients characteristics predicting LTS (Table 2). Body weight loss, disease extent, presence of liver metastases and increased white blood cells, neutrophils and lactic dehydrogenase (LDH) were found to be statistically significant predictors.

A multivariate analysis was performed by a logistic regression model using the variables with a $P < 0.30$, that is: loss of weight, Karnofsky PS, disease extent, lung, liver and bone metastatic sites, white blood cells, neutrophils and haemoglobin. The only factor found to be significantly related to LTS among the 486 patients included in the model was disease extent ($P = 0.002$), with a relative risk of 0.27 for metastatic disease compared to limited disease (95% CI 0.13–0.56).

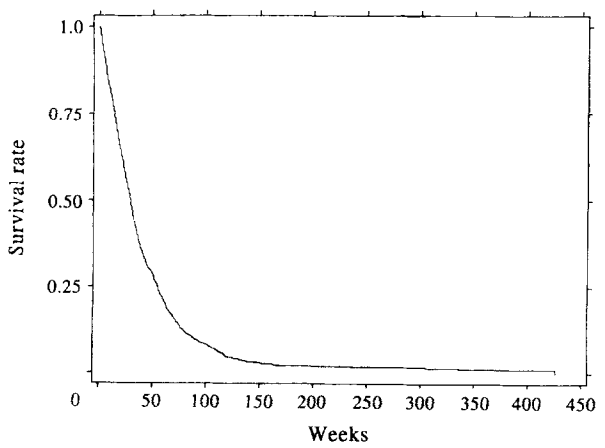

Figure 1. Overall survival curve for the whole study population (1052 NSCLC patients treated by chemotherapy).

Table 3. Survival status of the long-term survivors

Survival interval	Number of patients			Causes of death	
	Total	Alive	Died	Lung cancer	Other
2–3 years	44	4	40	35	5
3–4 years	7	2	5	5	—
4–5 years	7	6	1	1	—
5–6 years	2	1	1	—	1
6–7 years	3	2	1	—	1
7–8 years	2	1	1	1	—
Total	65	16	49	42	7

The predictive value of an objective response to chemotherapy for LTS was investigated in 723 patients who survived for at least 12 weeks and with a minimal follow-up period of 2 years. Of 65 LTS, 59 were evaluable for response, and of these 34 (58%) were objective responders, while 658 were not LTS, including 53 non-evaluable patients, 191 (32%) had an objective response. This difference was highly statistically significant ($P < 0.001$) with a 95% CI of 0.13–0.39 for the 0.26 difference in the objective response rate. A logistic regression model, using only objective response as explanatory variable for LTS, showed a relative risk of 2.95 (95% CI 1.71–5.08) in favour of responders.

In the multivariate analysis by the multiple regression model, objective response was added to the potential explanatory variables already mentioned. This analysis was performed on 354 patients. Two factors were found to be statistically associated with LTS with the same significant level ($P < 0.0002$): objective response with an odds ratio of 4.32 (95% CI 1.97–9.43) in favour of responders and disease extent with an odds ratio of 0.22 (95% CI 0.09–0.49) in favour of no metastatic disease.

The present survival status of the 65 LTS is reported in Table 3: 49 died, due to lung cancer in the majority (42, 86%) or from other or unknown causes in 7 (cardiac arrest 1, suicide 1, stroke 1, colon cancer 1, cause of death was not identified in 3 patients). 14 patients survived for more than 4 years, and 7 for more than 5 years. Their individual characteristics are given in Table 4. 9 (64%) of them were responders to chemotherapy; 4 had no change, and 1 was not evaluable because treatment was discontinued for toxicity. All but 2 had limited disease; these 2 patients with metastatic disease had bone lesions as the only metastatic location. All but 3 were treated after chemotherapy by surgery (2), chest irradiation (6) or both modalities (3). None of the 5-year survivors were treated by chemotherapy alone. The 8-year survivor died from bone metastases due to lung cancer.

DISCUSSION

In 1052 patients, included in the consecutive trials of the ELCWP investigating chemotherapy with platinum derivatives for advanced NSCLC, only low actuarial 2-year and 5-year survival rates, respectively, 7.4 and 1.8%, were observed. 65 patients were alive at 2 years, including 14 at 4 years and 7 at 5 years. The majority of the patients who survived for more than 2 years died from lung cancer. Only 2 survivors above 4 years had initially metastatic disease (bone lesions), and all the patients surviving for ≥5 years had limited disease, and were treated after chemotherapy with chest irradiation and/or surgery. The longest survivor died after 426 weeks from lung cancer.

There are very few studies in the literature reporting on long-

Table 4. Individual characteristics of the 14 patients with >4 years survival

Patient no.	Survival (weeks)	Alive/died	Cause of death	Pretherapeutic characteristics: Prior therapy	Extent	Metastatic sites	Weight loss	Chemotherapy regimen	Response to chemotherapy	Further treatment
4 years										
1	216	Alive	—	—	LD	—	0	CDDP(120)–VP16	PR	—
2	229	Alive	—	—	LD	—	0	CDDP(120)–VP16	CR	Chest RT
3	230	Alive	—	—	LD	—	0	CDDP(120–VP16	Inevaluable (toxicity too high)	Surgery+chest RT
4	235	Died	Lung cancer	—	MD	Bone	0	CDDP(60)–VP16	NC	Chest RT
5	237	Alive	—	—	LD	—	0	CDDP–5FU–MMC–VDS	PR	Surgery+chest RT
6	246	Alive	—	Bone RT	MD	Bone	0	CDDP(60)–VP16	PR	—
7	249	Alive	—	Surgery + chest RT	LD	—	0	CDDP–5FU–MMC–VDS	NC	Chemotherapy
5 years										
8	301	Alive	—	—	LD	—	0	CBDCA+VP16	CR	Surgery
9	305	Died	Unknown	—	LD	—	0	CDDP–VP16–VDS	NC	Chest RT
6 years										
10	336	Died	Colon cancer	—	LD	—	0	CDDP(60)–VP16	PR	Chest RT
11	347	Alive	—	—	LD	—	>5%	CDDP(120)–VP16	PR	Chest RT
12	350	Alive	—	—	LD	—	0	CDDP(120)–VP16	PR	Surgery+chest RT
7 years										
13	408	Alive	—	—	LD	—	>5%	CDDP	NC	Surgery
8 years										
14	426	Died	Lung cancer	—	LD	—	0	CDDP(120)–VP16	PR	Chest RT

LD, limited disease; MD, metastatic disease; RT, radiotherapy; CDDP, cisplatin; (120), 120 mg/m^2; (60), 60 mg/m^2; 5FU, 5 fluorouracil; MMC, mitomycin C; VDS, vindesine; CBDCA, carboplatin; PR, partial response; CR, complete response.

term survival after chemotherapy for advanced NSCLC [5, 6]: almost all have a relatively short follow-up; the median survival is usually around 6 months with less than 10% of the patients surviving for more than 2 years. In the ECOG report [5], 4% of the patients survived for more than 2 years. In the SWOG report [6], only the ≥1 year survival rate was given (16%). This rate was, respectively, 19% in the ECOG study and 26% in our present report. In none of the North American studies are details given on the characteristics of the LTS.

We identified, by univariate analysis, the following significant, positive, pretreatment, predicting factors for LTS (≥2 years): no major body weight loss, limited disease, absence of liver metastases, normal white blood cells, neutrophils and LDH levels, and, by multivariate analysis, only limited disease. In the ECOG report, a logistic regression model identified as discriminating factors in favour of a >1 years survival the following, by decreasing order of importance: initial ECOG PS of O, no bone metastases, female sex, no weight loss within the previous 6 months, no metastases to subcutaneous tissue, non-large cell histology, no prior symptom of shoulder or arm pain and no metastases to the liver. These data cannot easily be compared with our findings because the ECOG patients had only metastatic disease, and because we do not have the same pretreatment characteristics in our database. In the SWOG report, where patients with non-metastatic disease were also included, a prognostic factor analysis was not specifically performed for LTS. The predicting factors that we identified have already been identified when prognostic factor analysis has been performed for overall survival in patients with advanced NSCLC [5, 6, 18–21]. In the study by Stanley [18] reported in 1980 and performed on more than 5000 patients with inoperable lung cancer, the three most significant factors affecting survival were the Karnofsky initial PS, extent of disease and weight loss in the previous 6 months. We did not identify PS as significant, probably because our group of patients was selected: only those with a PS ≥ 60 were eligible for the protocols. Increased LDH has been reported to be significant in other trials [6, 19–21]. An increased white blood cells count, rarely investigated as a prognostic factor for survival, was found to be significant in a Danish report [21].

We attempted to determine if response to initial chemotherapy was a prognostic factor for LTS, by excluding all the patients who died during the first 12 weeks, before the evaluation of response. The exclusion of these patients was performed in order to avoid the criticism that patients who would have to be considered as non-responders because they did not survive (for

any reason) sufficiently enough to reach the response evaluation point were included in the ≤2 years survivor group. Inclusion of these patients would have underestimated the response rate in the short survival patients group, and consequently have improved our results in favour of the long-term survivors. Among the 723 patients having survived at least 12 weeks, objective response to chemotherapy was found to be a highly significant, prognostic factor. A multivariate analysis performed on 354 evaluable patients showed that response and disease extent were both identified as equally significant predictors: the responders and the patients with limited disease were four times more likely to survive 2 years than the non-responders and the patients with metastic disease. To our knowledge, this approach has not been used by others to determine the role of response as predictor for LTS. Response to therapy has, however, been investigated as a prognostic factor for overall survival by O'Connell and colleagues [19], taking into account only patients who survived more than 70 days; response was also found to be strongly associated with better survival.

The identification of objective response as a predictor for LTS does not demonstrate that chemotherapy is responsible for LTS. Such a statement could only be supported by an appropriately designed, randomised trial. Currently, the role of chemotherapy in the management of NSCLC is considered to have a small palliative effect [2], and its impact on survival in comparison to the best supportive care is still controversial, even if cisplatin is used [4].

In our series, the 7 survivors of ≥5 years, who all had limited disease initially, had undergone chest irradiation or surgery after initial chemothrapy. In such cases, chemotherapy can retrospectively be considered as a neoadjuvant therapy and, therefore, it is impossible to determine whether it added to the radical treatment given later. Combined modality treatment for non-metastatic NSCLC still remains an investigational topic [22–25].

In conclusion, LTS rates after initial chemotherapy containing platinum derivatives are low in patients with advanced NSCLC. The two best predicting factors for LTS are non-metastatic disease and response to chemotherapy; however, none of the >5 years survivors had been treated only with chemotherapy. Our study does not demonstrate that cisplatin-containing chemotherapy alone can cure patients with advanced NSCLC.

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