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Six *vs* twelve cycles for complete responders to chemotherapy in small cell lung cancer: definitive results of a randomized clinical trial

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Six vs *twelve cycles for complete responders to chemotherapy in small cell lung cancer: definitive results of a randomized clinical trial. B. Lebeau, Cl. Chastang, P. Allard, J. Migueres, F. Boita, D. Fichet and the "Petites Cellules" group.*

ABSTRACT: Of 320 patients with small cell lung cancer (SCLC) entered into a clinical trial of chemotherapy between January 1983 and September 1985, 106 patients achieved a complete response. The induction chemotherapy used was lomustine 60 mg·m^{-2} *p.o.*, cyclophosphamide 1 g·m^{-2} *i.v.*, doxorubicin 45 mg·m^{-2} *i.v.* and etoposide 150 mg·m^{-2} *i.v.*, every four weeks. Lomustine was only given for the first three cycles. Seventy nine of the 106 patients still in complete response after six chemotherapy cycles were subsequently randomized to receive either six more cycles or no more treatment until relapse. In this group of 79 patients, a difference was shown from the time of inclusion between the 51 patients with limited disease and the 28 patients with disseminated disease, with overall median survivals of 395 and 165 days, respectively, (p=0.0002). No difference was shown between the two treatment groups: the median survival was 332 days from the time of second randomization with a two year survival rate of 28% for the patients randomized to receive six more cycles and 246 days and 22% for those randomized to receive no more treatment (add 147 days to obtain overall median survival). Continuing chemotherapy for more than six cycles to patients in complete response did not improve survival.

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The optimal duration of chemotherapy in small cell lung cancer (SCLC) is an unsolved problem [1]. More than ten years ago, when it became clear that the use of aggressive combination chemotherapy was necessary to obtain best results, treatment was given for at least one year and often much longer [2]. In breast cancer and in Hodgkin's lymphoma, duration of chemotherapy has been reduced to avoid long-term complications (other cancers, leukaemias) and to improve the quality of life. No change in the median survival was observed. More recently, leukaemias and second cancers have been reported in long-term survivors of SCLC [3, 4]. Long survival times were obtained for patients in whom treatment was stopped because of toxicity after 4, 6 or 8 cycles [5, 6]. We have reported the case of a patient who received three courses of chemotherapy and who obtained a long disease-free survival [7]; he is still alive 8 yrs after this short duration treatment. To assess the effect of treatment duration, we were among the first to initiate, in 1983, a multicentre randomized clinical trial on this subject.

Materials and methods

Eligibility

Histological diagnosis was established at the clinical centre to which the patient was referred. Slides were sent to a panel of pathologists to confirm the diagnosis. Patients with no prior therapy (surgery, radiotherapy or chemotherapy), no prior malignancy, leucocyte count ≥3,000·μl^{-1}, platelet count ≥100,000·μl^{-1}, no renal failure, coronary insufficiency or heart failure, no aspirin allergy or gastroduodenal ulcer (for aspirin trial, see later), no potential follow-up difficulties (psychological or social problems) were eligible. No limits of age or general status were defined.

Baseline studies

Before inclusion in the trial, all patients had to undergo a complete interview concerning medical history, a physical examination, chest X-rays, electrocardiography, fibreoptic bronchoscopy, brain computed

tomographic (CT) scan or isotope scan, complete blood count, erythrocyte sedimentation rate, creatinine and electrolytes, calcium, alkaline phosphatases and transaminases. Other examinations were optional dependent on the facilities available at each centre, which had to be consistent in its policy: isotope liver scan or abdominal CT scan or liver ultrasonography, isotope bone scan, bone marrow aspiration and biopsy, tumour markers (principally carcinoembryonic antigen (CEA)).

Randomization

Randomization was made by telephoning the trial centre. An initial randomization was made to receive or not to receive aspirin. All patients, however, received six courses of combination chemotherapy. Those patients who achieved a complete response by the end of the sixth course of chemotherapy entered a second randomization, which was stratified according to centres and according to aspirin treatment. They received six more courses of the same chemotherapy (Group 1) or no further chemotherapy until relapse (Group 2).

Therapy

Chemotherapy was given on a single day every four weeks. Four agents were administered for the first three cycles: lomustine 60 $mg \cdot m^{-2}$ orally, cyclophosphamide 1 $g \cdot m^{-2}$ *i.v.*, doxorubicin 45 $mg \cdot m^{-2}$ *i.v.* and etoposide 150 $mg \cdot m^{-2}$ *i.v.*; lomustine was subsequently stopped. If progression occurred during the first two cycles, patients were to be given other therapies (thoracic radiotherapy for limited disease and other chemotherapy for disseminated disease). Aspirin was given to 163 patients 1 $g \cdot day^{-1}$ for 18 months and was prohibited for 157 others according to first randomization. Duration of chemotherapy depended on response: complete responders (CR) received 6 or 12 cycles, partial responders (PR) were treated until progression, non-responders (NR) received other treatments which were chosen independently but homogeneously in each centre. In case of haematological toxicity (leucocyte count $<3{,}000 \cdot \mu l^{-1}$ and platelet count $<100{,}000 \cdot \mu l^{-1}$), chemotherapy was deferred from one week to another without exceeding eight weeks from the last treatment; a 50% dose reduction was made at this time.

Cranial radiotherapy was administered to those patients with brain metastases present at diagnosis, at a dose of 40 to 45 grays, generally over four weeks. Prophylactic irradiation of the brain was performed in all those whose primary tumour responded 3 or 4 months after starting chemotherapy.

Patient assessment during and after therapy

Interval histories, clinical and thoracic X-ray examinations and blood counts were checked at least monthly during the first year, every two months during the second year and quarterly thereafter. Fibreoptic bronchoscopy was performed quarterly during the first year, then twice a year or in case of suspected relapse, with biopsies of the initial site of lesions.

Responses were defined as CR, PR or NR according to the World Health Organization (WHO) criteria [8], or not evaluable (NE) if the patient did not receive adequate treatment or died before the first assessment. Fibreoptic bronchoscopy was required for local confirmation of CR.

Treatment on relapse

For patients who relapsed it was advised to use the same chemotherapy after a disease-free survival of, usually, at least six months, but no further treatment was an option after progression or rapid relapse. For patients relapsing at the primary site only, or with superior vena cava obstruction syndrome, thoracic radiotherapy was given.

Statistical analysis

For censored criteria (survival and disease-free interval) the Kaplan-Meier estimate and the log-rank test were used. Analysis was made on an intention-to-treat basis.

Results

Patient characteristics

From January 1983 to September 1985, 320 patients were included by 23 centres. There were 151 patients with limited disease and 169 patients with disseminated disease. According to the protocol, 17 were excluded after review by the panel of pathologists because they did not have SCLC (eight limited and nine disseminated).

After six cycles of chemotherapy, 79 patients from 10 centres still in CR were randomized for the second time. Their characteristics are summarized in table 1.

Table 1. – Characteristics of the 79 complete responder patients randomized for treatment duration

		Group 1	Group 2	Total
Sex:	Male	35	32	67
	Female	8	4	12
Age:	>70 yrs	7	7	14
	<70 yrs	36	29	65
Performance status:	>70	38	32	70
(Karnofsky index)	<70	5	4	9
Disease stage:	Limited	31	20	51
	Extensive	12	16	28

Group 1: six courses more; Group 2: no more treatment.

The sex ratio was male/female 5.5/1. The mean age was 60±9 yrs and 14 (18%) were >70 yrs old. There were 51 patients with limited disease (35% of the initial sample) and 28 with disseminated disease (17% of the initial sample).

Response to therapy and survival (initial sample: table 2)

Response was observed in 85% of the 303 evaluable patients (40% CR and 45% PR). In those with limited disease, the response rate was 89% (50% CR and 39% PR). Thirty six patients were not evaluable for response, for various reasons: 28 early deaths (15 rapidly progressive disease in less than four weeks, 10 cases of marrow aplasia following the first two cycles and three cases of cardiovascular disease), six patients refused treatment and two patients died before they received treatment, soon after randomization.

Median survival was 41 weeks for the 303 patients; it was 32 weeks for extensive disease and 53 weeks for apparently limited disease.

Table 2. – Survival of the 303 patients with SCLC (01 PC 83 trial)

	Overall population	Limited stage	Extensive stage
Patient n	303	140	163
Median survival weeks	41	53	32
One year survival rate %	37	54	22
Two year survival rate %	10	16	4

SCLC: small cell lung cancer.

Response, disease-free survival and median survival of the complete responders (fig. 1)

The mean interval between initial entry and the second randomization was 21 weeks. One hundred and six patients were considered to be in CR but only 79 entered the second part of the study. Twenty seven were not included: 10 for recurrence after an initial CR, 10 for protocol violation, five died in CR before reaching the second randomization (four toxic deaths) and two patients only achieved CR after the sixth cycle of chemotherapy.

For the 36 patients in group 2, no problem arose until relapse, but for the 43 patients in group 1, only 21 completed treatment: 16 developed disease progression, five refused chemotherapy after 6, 6, 8, 8 and 9 cycles and one patient died of myelosuppression after the seventh cycle.

Disease-free survival until relapse was 40 weeks in group 2 and 54 weeks in group 1. Median survival was 246 days from the second randomization for group 2 and 332 days for group 1 (*i.e.* 56 and 68 weeks after the first randomization, respectively). This difference was not significant (p=0.41). Disease stage at diagnosis was an important prognostic factor in spite of subsequent CR: median survival of 404 days for patients with limited disease and 167 days for those with extensive disease (p=0.0002) (fig. 2). Two year survival rates were estimated at 22% for patients randomized to receive no more treatment and 28% for patients randomized to receive six more cycles. At the present time, with a minimal follow-up of three years, only five patients are still alive, one in group 2 and four in group 1. It is interesting to note that of the four patients alive in the six more cycles group, two refused more treatment after eight and nine courses, respectively.

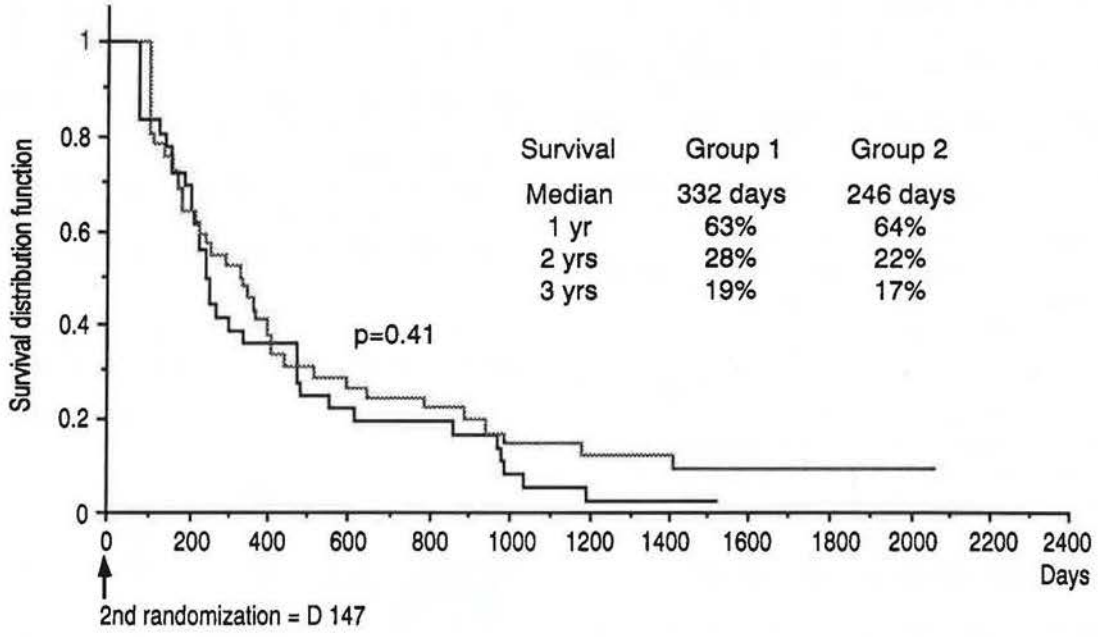

Fig. 1. – Crude survival of 79 patients with small cell lung cancer (SCLC) in complete response after six courses of chemotherapy, randomized between six more cycles of chemotherapy (Group 1, ... , n=43) and no more treatment until relapse (group 2, ——— , n=36).

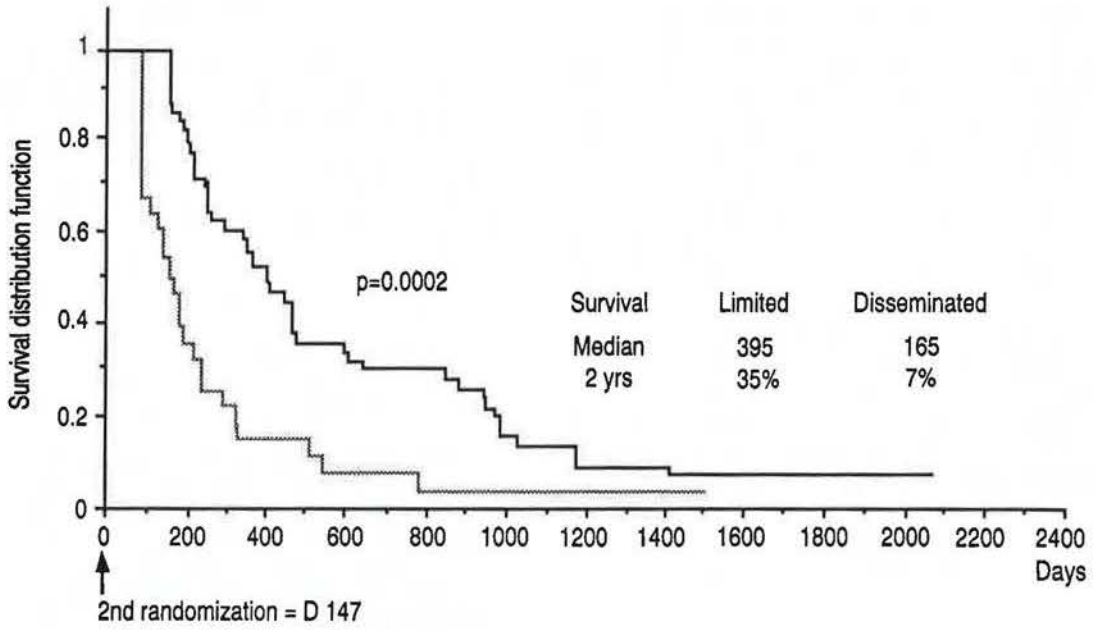

Fig 2. – Crude survival of 79 patients with small cell lung cancer (SCLC) in complete response after six courses of chemotherapy, comparing limited disease (——, n=51) and disseminated disease (......, n=28).

Treatment on relapse (table 3)

Most patients were treated on relapse. In group 2, 30 out of 36 patients received chemotherapy; of the six remaining, three received thoracic irradiation alone, two died from a cause other than SCLC and one died from cerebral metastases. In group 1, only 20 out of 43 received chemotherapy on relapse, as most progressed during their second chemotherapy regimen; six patients with a loco-regional relapse received thoracic irradiation, four were too ill to endure cytotoxics, two died from other causes, one died from the toxic effects of chemotherapy and two are still disease-free. The range of overall numbers of chemotherapy courses received by the two groups is the same: 6 to 21, but the mean number is nonsignificantly greater in the six courses more treatment group (group 1): 10.9 courses, than in group 2: 9.6 courses.

Table 3. – Treatment on relapse

	Group 1	Group 2	Total
Chemotherapy on relapse	20	30	50
Thoracic radiotherapy on relapse	12	11	23
Mean number of total chemotherapy courses	10.9	9.6	10.3

Group 1: six courses more; Group 2: no more treatment.

Discussion

Almost all combination chemotherapy obtains similar response rates (80–90%) to those achieved by our protocol, which was based on that of AISNER *et al.* [9]. We added lomustine because this drug had a good response rate when used alone in SCLC [10]. We did not use thoracic radiotherapy for limited stage disease because, in 1982, a review of trials comparing chemotherapy alone to chemotherapy plus radiotherapy did not show any survival advantage; actually, thoracic radiotherapy seems to have been used in limited diseases [11].

Several studies have addressed the question of the optimal duration of chemotherapy, particularly in responding populations. Intensive chemotherapy induction without maintenance has been shown to provide acceptable survival data [12, 13]. A randomized study of 497 patients found no difference between those patients who received maintainance chemotherapy and another group in whom treatment was stopped after six cycles [14]. In this study, only the 265 responders were included in the randomization and separate analyses of subgroups were made between the partial and complete responders. The median survival period from the date of randomization was 42 weeks for complete responders receiving twelve courses of chemotherapy and 30 weeks for no maintainance chemotherapy ($p<0.05$). This suggests an advantage for the addition of six more courses of chemotherapy. It is possible that this would not have been seen in our study because of the smaller number of patients included. However, the ratio of risks of death in the treatment groups was estimated showing an increase of 5% survival at one year. Thus, a total of 1,136 deaths would be required to show such an increase, assuming one-sided test with $\alpha=0.05$ and a power of 0.80. Given the observed number of deaths in our study we could show an increase of 50–68% in overall survival.

Most studies reached the same conclusion, that the initial response to chemotherapy is the most important factor determining survival. The addition of a further

seven courses to those patients responding (CR or PR) to five initial treatments was compared to conservative therapy only and showed no advantage for the additional seven chemotherapy courses [15]. Another large study of 616 patients gave four or eight courses of initial chemotherapy with or without further chemotherapy at relapse [16]. This showed relapse chemotherapy to prolong survival only if relapse occurred in those patients receiving four courses of initial chemotherapy, but made no impact if the patient had received eight initial courses. Four courses of chemotherapy alone with no further treatment at relapse, was inferior to eight initial courses.

Although the numbers of patients in the current study are small it adds to the current bank of data that suggests that even for responding patients, additional chemotherapy adds little benefit to survival.

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Table 4. – "Petites Cellules" Group 01 PC 83 trial January 1, 1983 to September 30, 1985

Centres	Pts n	Authors
Hôtel-Dieu, Paris	51	B. Lebeau, J.M. Brechot, J. Ameille, O. de Fenoyl, J. Rochemaure
Troyes	27	P. Meekel, J.P. Hurdebourg
Amiens	26	J.F. Muir, P. Aubry, A. Hermant, S. Ndarurinze
Le Mans	23	F.X. Lebas, J. Malbos, Y. Piron, S. Girard, R. Ras
Salpêtrière, Paris	21	Ph. Chaumier, B, Dautzenberg, Ch. Sors
La Rochelle	21	J. Vincent, D. Lambard
Dijon, CHU	20	F. Massin, O. Reybet-Degas, P. Camus, L. Jeannin
Montfermeil	19	C. Fabre, G. Hinaut
Dreux	14	D. Fichet, F. Martin
Toulouse (Rangueil)	14	J. Migueres, R. Vetillard, M. Krempf, R. Escamilla
Percy, hôpital militaire	14	P. Allard, P. L'Her, H. Demuizon, F. Natali, J. Kermarec
Poitiers	13	M. Underner, F. Boita, F. Patte
Angers	12	J. Berruchon, M. Oury, E. Tuchais
St Antoine, Paris	9	J.P. Derenne, T. Lepage, B. Malamud, M.J. Masanes
Creil	8	M.J. Botto, P. Charvolin
St Joseph, Paris	7	J. Sauvaget, J.L. Rebishung, M. Mellat
Bourges	6	G. Desrivot
Dôle	5	J. Ranfaing
St Germain en Laye	4	N. Robillard, P. Leclerc
Vierzon	2	M. Mornet
Beauvais	2	J.C. Lattaignant, C. Mascret
Dijon, hôpital militaire	1	P.J. Hardel
Royan	1	P. Papeix

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