Standard Versus Intensified Chemotherapy With Granulocyte Colony-Stimulating Factor Support in Small-Cell Lung Cancer: A Prospective European Organization for Research and Treatment of Cancer–Lung Cancer Group Phase III Trial—08923

By Andrea Ardizzoni, Vivianne C.G. Tjan-Heijnen, Pieter E. Postmus, Erica Buchholz, Bonne Biesma, Hanna Karnicka-Mlodkowska, Rafal Dziadziuszko, Jos Burghouts, Jan P. van Meerbeeck, Steven Gans, Catherine Legrand, Channa Debruyne, Giuseppe Giaccone, and Christian Manegold for the European Organization for Research and Treatment of Cancer–Lung Cancer Group

Purpose: **To assess the impact on survival of increasing dose-intensity (DI) of cyclophosphamide, doxorubicin, and etoposide (CDE) in small-cell lung cancer (SCLC).**

Patients and Methods: **Previously untreated SCLC patients were randomized to standard CDE (cyclophosphamide 1,000 mg/m² and doxorubicin 45 mg/m² on day 1, and etoposide 100 mg/m² on days 1 to 3 every 3 weeks, for five cycles) or intensified CDE (cyclophosphamide 1,250 mg/m² and doxorubicin 55 mg/m² on day 1, and etoposide 125 mg/m² on days 1 to 3 with granulocyte colony-stimulating factor [G-CSF] 5 μg/kg/d on days 4 to 13 every 2 weeks, for four cycles). Projected cumulative dose was almost identical on the two arms, whereas projected DI was nearly 90% higher on the intensified arm. Two hundred forty-four patients were enrolled. The first 163 patients were also randomized (2 × 2 factorial design) to prophylactic antibiotics or placebo to assess their impact on preventing febrile leukopenia (FL). This report focuses on chemotherapy DI results.**

Results: **With a median follow-up of 54 months, 216 deaths have occurred. Actually delivered DI on the intensified arm was 70% higher than on the standard arm. Intensified CDE was associated with more grade 4 leukopenia (79% *v* 50%), grade 4 thrombocytopenia (44% *v* 11%), anorexia, nausea, and mucositis. FL and number of toxic deaths were similar on the two arms. The objective response rate was 79% for the standard arm and 84% for the intensified arm (*P* = .315). Median survival was 54 weeks and 52 weeks, and the 2-year survival rates were 15% and 18%, respectively (*P* = .885).**

Conclusion: **A 70% increase of CDE actual DI does not translate into an improved outcome in SCLC patients.**

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COMBINATION CHEMOTHERAPY represents the mainstay of small-cell lung cancer (SCLC) treatment.[1] Despite many years of intensive research, the role of chemotherapy dose intensification as a way to improve the prognosis of SCLC remains controversial. Classic high-dose chemotherapy plus autologous bone marrow transplantation has been abandoned because of excessive toxicity and contradictory results,[2] although recent developments in blood products have generated a renewed interest in this field.[3,4] Moderate chemotherapy dose increase has led to conflicting results,[5-7] and maintaining standard full dose, by avoiding dose-reduction with prophylactic granulocyte colony-stimulating factor (G-CSF), has not been shown to produce any significant survival benefit.[8,9] In 1984, Hryniuk and Bush[10] developed the concept of "dose-intensity" (DI), defined as the amount of chemotherapy delivered per unit time, as a better instrument to correlate intensity of chemotherapy with the clinical outcome. A number of retrospective studies confirmed that chemotherapy DI correlates with objective response and survival in several solid tumors and hematologic malignancies.[11] The concept of DI implies that chemotherapy intensification can be achieved either by increasing dose size, ie, the dose of chemotherapy per cycle (high-dose chemotherapy) or by increasing dose density, ie, shortening intervals between doses (dose-dense or accelerated chemotherapy). With the prophylactic use of myelopoietic growth factors, chemotherapy

From the Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy; University Medical Centre Nijmegen, Nijmegen; Vrije Universiteit Medical Centre, Amsterdam; Bosch Medicentrum, 's-Hertogenbosch; Ziekenhuis St Jansdal, Harderwijk; and Erasmus MC, Rotterdam, the Netherlands; Thoraxklinik Rohrbach, Heidelberg, Germany; PCK Maritime Hospital, Gdynia; and Medical University of Gdansk, Gdansk, Poland; and European Organization for Research and Treatment of Cancer Data Center, Brussels, Belgium.

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Address reprint requests to Andrea Ardizzoni, MD, Medical Oncology I, Istituto Nazionale per la Ricerca sul Cancro, Largo Rosanna Benzi 10, 16132 Genova, Italy; email: andrea.ardizzoni@istge.it.

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intervals can be shortened by about 30%, thereby increasing DI by nearly 50%, in many tumor types and with different chemotherapy regimens.[12-15]

In a retrospective study, chemotherapy DI has been shown to correlate with survival outcome in SCLC, particularly in extensive disease (ED) patients treated with cyclophosphamide, doxorubicin, and etoposide (CDE).[16] The CDE chemotherapy regimen is widely used in Europe to treat SCLC and has long been considered as the standard reference regimen by the European Organization for Research and Treatment of Cancer (EORTC)–Lung Cancer Group.[17]

In a pilot study of our group,[18] it was feasible to deliver a 25% higher CDE dose every 2 weeks (instead of the usual CDE regimen every 3 weeks) with the support of prophylactic G-CSF, on an outpatient basis. The present multicenter randomized study was designed to assess the impact of such a DI increase on survival of previously untreated SCLC patients.

PATIENTS AND METHODS

Patient Selection

Patients had to meet all of the following inclusion criteria: histologic or cytologic diagnosis of SCLC, presence of ED or limited disease (LD), measurable or assessable disease, no prior chemotherapy, Eastern Cooperative Oncology Group performance status (PS) 0 to 1, age between 18 and 69 years, ability to undergo protocol treatment, WBC counts $\geq 4 \times 10^9$/L, platelet (PLT) counts $\geq 100 \times 10^9$/L, hemoglobin (Hb) $\geq$ 6.0 mmol/L, creatinine $\leq$ 140 μmol/L, and bilirubin less than 35 μmol/L.

Patients were excluded in case of symptomatic cerebral metastases, active infection or fever $\geq$ 38.3°C, uncontrolled hypertension, symptomatic cardiovascular disease within 3 months before enrollment, previous malignancy (except for basal or squamous cell skin carcinoma or adequately treated carcinoma-in-situ of the cervix), and any evidence or history of hypersensitivity or other contraindications for the drugs used in this trial. The investigational protocol was approved by the EORTC Protocol Review Committee and by the ethical committee of each participating institution. Written informed consent was obtained from each patient according to national regulations.

For each patient, baseline evaluation consisted of medical history, physical examination, laboratory investigations, chest x-ray and computed tomography scan, computed tomography scan or ultrasound of the upper abdomen, bronchoscopy, and bone scan. As soon as a measurable or assessable lesion was detected to diagnose ED, no further investigations were required by the protocol. In case of unexplained thrombocytopenia or leukocytopenia, a bone marrow biopsy had to be performed to rule out bone marrow metastases.

Study Design

In this phase III trial, SCLC patients were randomized to standard or intensified chemotherapy to assess the impact of DI increase on survival. Secondary end points were response rate and risk of toxic deaths. Although not predefined as an end point by the protocol, the impact of DI increase on progression-free survival, defined as the interval between randomization and disease progression or death, was also assessed.

The first 163 patients were also randomized, with a 2 $\times$ 2 factorial design, to prophylactic antibiotics (ciprofloxacin 750 mg plus roxithromycin 150 mg bid on days 4 to 13) or placebo. The primary end point of this comparison was the incidence of febrile leukopenia (FL) in the first chemotherapy cycle. The antibiotic-placebo randomization was prematurely stopped following the recommendation of the Independent Data-Monitoring Committee, as an interim analysis showed a 50% reduction in the incidence of FL by the use of prophylactic antibiotics. Thereafter, all patients enrolled on both standard and intensified arms received prophylactic antibiotics (ciprofloxacin and roxithromycin). The results of the antibiotic comparison on this trial have been reported elsewhere.[19] We report here the final results concerning the impact of DI increase on the clinical end points.

Chemotherapy Regimen

Standard CDE chemotherapy consisted of cyclophosphamide 1,000 mg/m^2 on day 1, doxorubicin 45 mg/m^2 on day 1, and etoposide 100 mg/m^2 on days 1 to 3 given intravenously every 3 weeks for five cycles. Intensified CDE chemotherapy consisted of cyclophosphamide 1,250 mg/m^2 on day 1, doxorubicin 55 mg/m^2 on day 1, and etoposide 125 mg/m^2 on days 1 to 3 given intravenously every 2 weeks for four cycles.[18] The total dose of chemotherapy was approximately the same on both arms, but the planned DI was nearly 90% higher on the intensified arm. Chemotherapy was discontinued earlier in case of progressive disease, treatment failure, patient refusal, or unacceptable toxicity.

Blood counts were measured on days 8, 12, 15, 19, and 22 during standard CDE and on days 8, 12, and 15 during intensified CDE. Dose adjustments were made on the basis of day-1 blood counts and on WBC and/or PLT nadir. Full-dose chemotherapy was given in case of WBC counts more than 3.0 $\times$ 10^9/L and PLT counts more than 100 $\times$ 10^9/L at day 1 of every cycle.

On the standard arm, the treatment was delayed for 1 week in case of WBC counts less than 2.0 $\times$ 10^9/L and/or PLT counts less than 75 $\times$ 10^9/L, and a 50% dose reduction was given in case of WBC counts between 2 and 3 $\times$ 10^9/L and PLT counts between 75 and 100 $\times$ 10^9/L on day 1. For nadir WBC counts of less than 0.5 $\times$ 10^9/L and/or nadir PLT counts less than 25 $\times$ 10^9/L, the doses of all drugs had to be reduced to 75% in subsequent cycles.

On the intensified arm, treatment was delayed in case of low day-1 blood counts. However, in case of reduced WBC counts (2 to 3 $\times$ 10^9/L) and/or PLT counts (75 to 100 $\times$ 10^9/L) after a 1- to 2-week delay, a 50% dose reduction was applied. No dose reductions were allowed for nadir blood values, unless there was grade 4 hematologic toxicity for more than 7 days or in case of serious complications such as bleeding resulting from thrombocytopenia. In this case, a 25% dose reduction was prescribed. For nadir WBC counts of less than 1.0 $\times$ 10^9/L and/or nadir PLT counts of less than 25 $\times$ 10^9/L lasting for over 14 days, protocol treatment was discontinued.

G-CSF

On the intensified arm, G-CSF (filgrastim) was given on days 4 to 13 at a dose of 300 μg/d if body weight was $\leq$ 75 kg and at a dose of 5 μg/kg/d if body weight was more than 75 kg.

Posttreatment Procedures

All abnormal pretreatment investigations had to be repeated, except for bone scan, at the end of treatment. Repeated bronchoscopy was not required to confirm a radiologic complete response.

Sequential thoracic radiation therapy in responding LD patients at the end of chemotherapy was allowed, provided that each institute had to follow one strategy throughout the study. Prophylactic cranial irradiation at the end of chemotherapy in case of complete response in LD patients was also allowed according to institutional policy.

Patients were followed every 6 weeks by physical examination and chest x-ray. In case of progression, radiotherapy or second-line systemic therapy was allowed. In case of relapse more than 3 months after the last chemotherapy cycle, reinduction with standard-dose CDE was recommended. In case of relapse within 3 months, the use of second-line therapy was left to the discretion of the responsible physician.

Statistical Considerations

For sample size estimation, it was calculated that a total of 192 deaths would permit the detection of an increase in median survival from 52 weeks on the standard CDE arm to 78 weeks on the intensified CDE arm at a two-sided significance level of 5% and with a power of 80%. This corresponds to an increase in 1-year survival from 50% to 63%. A total of 240 patients (60 in each stratum) needed to be randomized to obtain this number of events. Randomization was performed using the minimization technique, stratifying patients according to institution, age ($\leq$ 60 years *v* $>$ 60 years), and stage of disease (LD *v* ED).[20]

The original protocol did not plan an interim analysis. However, after 163 patients were randomized, concerns were raised with respect to differences in the incidence of FL between trial arms, and the group decided to perform an unplanned interim analysis. This interim analysis investigated only the second question of the trial (impact of antibiotics *v* placebo on the incidence of FL). The results were submitted to the Independent Data-Monitoring Committee, which recommended to prematurely close the antibiotic versus placebo part of the protocol on ethical grounds. Following this recommendation, the protocol was amended to become a two-arm study (intensified *v* standard CDE) with all patients on both arms receiving prophylactic antibiotics.

The trial was analyzed as a 2 $\times$ 2 factorial design. Thus, for all statistical comparisons, the effect of CDE DI was analyzed after stratification for the type of prophylaxis (verum or placebo antibiotics). On the basis of the "intent-to-treat" principle, all analyses included all patients according to the treatment arm they were allocated to by randomization, irrespective of the treatment they actually received. All tests used in this report are two-sided tests.

DI was defined as the amount of drugs delivered per unit time (expressed in milligrams per meter squared per week).[10] The actually delivered DI was calculated as the ratio of the total dose (expressed in milligrams) per meter squared actually received by the patient divided by the actual total treatment duration expressed in weeks. In this calculation, the end of treatment duration is considered to be 3 weeks (standard arm) or 2 weeks (intensified arm) after day 1 of the last cycle of chemotherapy received. The relative DI was calculated as the ratio of the actually delivered DI to the DI planned by the protocol.

Overall survival and progression-free survival curves were estimated using the Kaplan-Meier technique.[21] Differences in survival between the two regimens (intensified *v* standard) were tested for statistical significance using the two-sided log-rank test at the 5% significance level.

To adjust for any confounding variables, retrospective stratification and the Cox regression analysis were performed in an exploratory spirit.[22] The Cox regression model was used with a two-sided test at the 5% significance level to test the prognostic value of each variable. A stepdown variable selection procedure was used for building the multivariate model.

Table 1. Patient Characteristics at Baseline

	Standard CDE (n = 119)		Intensified CDE (n = 125)	
	No.	%	No.	%
Age, years				
Median	59		59	
Range	33-69		35-70	
Sex				
Male	84	71	88	70
Female	35	29	37	30
ECOG PS				
0	41	35	53	42
1	78	66	72	58
Disease status				
LD	70	59	70	56
ED	49	41	55	44
Weight loss over past 3 months				
$\leq$ 5%	65	66	71	72
$>$ 5%	33	34	28	28

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Overall response rates (complete and partial), as secondary end points, have been compared between the two regimens (intensified *v* standard) with the Cochran-Mantel-Haenszel statistic. According to the protocol, incidence of toxic deaths should have been compared by using the log-rank test. However, because only a few toxic deaths occurred, comparisons by means of the Cochran-Mantel-Haenszel test have been performed instead.

Although not foreseen in the protocol, the rates of grade 3 or 4 toxicity on the two treatment arms were compared, using a stratified exact Wilcoxon-Mann-Whitney test. However, for most of the toxicity items, only a low rate of grade 3 and 4 toxicity was observed in this study and, therefore, no *P* values could be computed for these items. Reported *P* values, concerning differences in most frequent grade 3 and 4 toxicities, should be interpreted with caution in view of the multiple comparisons and the lack of sufficient power.

RESULTS

Patients

From October 1994 to May 1999, a total of 244 patients were enrolled by 16 European institutions. Among these, 119 patients (49%) were randomized to receive standard-dose CDE (80 patients receiving additional antibiotics and 39 patients receiving additional placebo), whereas 125 patients (51%) were randomized to receive intensified CDE (84 patients receiving additional antibiotics and 41 patients receiving additional placebo). One patient on the standard arm was considered ineligible because of an incorrect diagnosis. According to the intent-to-treat principle, this patient was included in all analyses and in all tables. Another patient was randomized twice because of a program error; therefore, the second randomization was excluded from all analyses and tables. Main patient characteristics are listed in Table 1. The two arms were well-balanced

Table 2. Reasons for Discontinuation of Protocol Treatment

	Standard CDE (n = 119)		Intensified CDE (n = 125)	
	No.	%	No.	%
Completion of protocol	94	79	101	81
Patient refusal	2	2	4	3
Protocol violation	3	3	0	0
Progressive disease	9	8	3	2
Toxicity	4	3	8	6
Early death,* malignancy	0	0	1	1
Early death,* toxicity	3	3	4	3
Early death,* other	1	1	0	0
Other	3	3	4	3

*Early death is defined as death occurring within 6 weeks from randomization.

in terms of baseline clinical characteristics and laboratory data (latter not shown). Briefly, 70% of the patients were males, median age was 59 years, 61% had a PS of 1, and 57% had LD.

Delivered Chemotherapy

Approximately 80% of patients on both arms completed the planned number of cycles (ie, five cycles on the standard CDE chemotherapy arm and four cycles on the intensified CDE arm) (Table 2). The median number of cycles received was five (range, one to six) on the standard arm and four (range, one to six) on the intensified arm. Although the reasons for discontinuation of protocol treatment were largely comparable for both treatment arms, more patients stopped treatment for progressive disease on the standard arm (8% *v* 2%), and more patients stopped protocol treatment because of toxicity (3% *v* 6%) on the intensified arm.

Dose reductions were used in approximately 10% of patients per cycle, on both arms (Table 3), whereas treatment delay was more often applied on the intensified arm compared with the standard arm. The main reason for dose modification was hematologic toxicity, especially thrombocytopenia.

The median relative DI for cycles actually delivered was 99% (range, 53% to 167%) of planned for the standard CDE arm and 90% (range, 50% to 106%) of planned for the intensified arm (Table 4). For each drug, the actually delivered DI for the intensified arm was about 70% higher than that of the standard arm. For each drug, the median delivered cumulative dose on the intensified arm was comparable to that of the standard arm.

Toxicity

The worst overall toxicity during all cycles is demonstrated in Tables 5 and 6. Myelosuppression was more severe in patients treated with intensified chemotherapy

Table 3. Delivered Chemotherapy

	Standard CDE (n = 119)		Intensified CDE (n = 125)	
Treatment Modification	No.	%	No.	%
Cycle 1				
Reduction	2	2	3	2
Delay	1	1	1	1
Not given				
Cycle 2				
Reduction	12	10	13	10
Delay	20	17	33	26
Not given	6	5	8	6
Cycle 3				
Reduction	7	6	10	8
Delay	13	11	49	39
Not given	13	11	17	14
Cycle 4				
Reduction	6	5	15	12
Delay	16	13	56	45
Not given	14	12	22	18
Cycle 5				
Reduction	11	9	0	0
Delay	20	17	1	1
Not given	23	19	124	99

(Table 5). Although overall incidence of grade 3 or 4 leukopenia was similar (over 90%) on the two arms, grade 4 toxicity (WBC count $< 1.0 \times 10^9$/L) occurred in 50% of patients on the standard-dose arm compared with 79% of patients on the intensified arm, despite the use of prophylactic G-CSF on this arm. The incidence of grade 3 or 4 thrombocytopenia and anemia was also higher for the intensified arm: 70% *v* 24% ($P < .001$) and 45% *v* 21% ($P < .001$), respectively. The median WBC nadir over all cycles was 1.0×10^9/L (range, 0.1 to 4.2×10^9/L) on the standard arm versus 0.5×10^9/L (range, 0 to 13.5×10^9/L) on the intensified arm, with a median duration of grade 4

Table 4. Delivered Chemotherapy

	Standard CDE (n = 119)		Intensified CDE (n = 125)	
	Median	Range	Median	Range
Actually delivered DI, mg/m^2/wk				
Cyclophosphamide	330	178-556	568	309-660
Doxorubicin	15	6-24	25	13-30
Etoposide	99	53-167	169	61-198
% of planned DI				
Cyclophosphamide	99	53-167	91	50-106
Doxorubicin	99	38-163	91	48-110
Etoposide	99	53-167	90	33-106
Delivered cumulative dose, mg/m^2				
Cyclophosphamide	4,974	971-5,750	4,964	1,211-5,848
Doxorubicin	222	44-258	217	53-257
Etoposide	1,492	291-1,725	1,489	123-1,754

Table 5. Worst Hematologic Toxicity (NCIC-CTC grade 3 or 4, per patient)

	Standard CDE (n = 119)		Intensified CDE (n = 125)	
	No.	%	No.	%
WBC*				
3	50	42	20	16
4	59	50	99	79
PLT†				
3	16	13	33	26
4	13	11	55	44
Hb‡				
3	19	16	51	41
4	6	5	5	4

NOTE. *P* values in comparisons of grade 3 or 4 toxicity of standard versus intensified CDE.

Abbreviation: NCIC-CTC, National Cancer Institute of Canada common toxicity criteria.

*$P = .380$.

†$P < .001$.

‡$P < .001$.

leukopenia episodes of 3 days on both arms. Thrombocyte nadirs were 84×10^9/L (range, 1 to 280×10^9/L) on the standard arm versus 27×10^9/L (range, 0 to 273×10^9/L) on the intensified arm. Hb nadir was 5.7 mmol/L (range, 1.8 to 8.9 mmol/L) on the standard arm versus 4.9 mmol/L (range, 2.9 to 9.2 mmol/L) on the intensified arm. Forty-one patients (34%) on the standard arm and 89 patients (71.2%) on the intensified arm received at least one transfusion (red cell or platelet or whole blood) during chemotherapy treatment.

FL occurred at least once in 24% of patients treated with standard-dose CDE chemotherapy versus 34% of patients treated with intensified CDE chemotherapy ($P = .102$). Nonhematologic toxicities were generally mild and similar on the two arms (Table 6). However, more patients on the intensified arm suffered from severe stomatitis/mucositis ($P = .024$).

Other Therapies After Protocol Treatment

After first-line CDE chemotherapy, further anticancer therapy was reported for 84% of patients on the standard-dose arm and for 86% of patients on the intensified arm. However, detailed information about type and compliance of further treatment was not prospectively collected. Chest radiotherapy was given in 54% and 52% of patients, respectively, and prophylactic brain radiotherapy was given in 19% and 20% of patients, respectively. Radiotherapy for progressive disease was given in 51% and 43% of patients, respectively. Maintenance therapies were given in 8% and 7% of patients, respectively.

Table 6. Worst Nonhematologic Toxicity (NCIC-CTC grade 3 or 4, per patient)

	Standard CDE (n = 119)		Intensified CDE (n = 125)	
	No.	%	No.	%
Febrile leukopenia*				
Yes	28	24	42	34
Hemorrhage				
3	0	0	1	1
4	0	0	2	2
Flu-like symptoms				
3	0	0	2	2
Renal and bladder				
3	0	0	2	2
Anorexia				
3	0	0	4	3
Nausea†				
3	2	2	7	6
Vomiting‡				
3	1	1	8	6
4	1	1	0	0
Stomatitis-mucositis§				
3	2	2	11	9
Diarrhea				
3	0	0	3	2
Liver				
3	2	2	2	2
Cardiac				
3	0	0	1	1
4	1	1	2	2
Pulmonary				
3	2	2	0	0
4	1	1	3	2
Neurologic				
3	2	2	1	1
Others				
3	2	2	7	6
4	1	1	2	2

NOTE. *P* values in comparisons of grade 3 or 4 toxicity of standard versus intensified CDE.

*$P = .102$.

†$P = .195$.

‡$P = .119$.

§$P = .024$.

Efficacy

Table 7 lists responses by treatment arm. There was no significant difference between the two arms. After a median follow-up of 49 months for the patients on the standard arm and 57 months for the patients on the intensified arm, 107 (90%) and 109 (87%) patients have died, respectively. Ninety-five (89%) versus 96 patients (88%) died of progressive disease. At the time of analysis, disease had progressed in 102 patients (85.7%) on the standard arm and 103 (82.4%) on the intensified arm. Toxic death was observed in three patients (3%) on the standard CDE arm and six

Table 7. Efficacy of Chemotherapy

	Standard CDE (n = 119)		Intensified CDE (n = 125)		
	No.	%	No.	%	*P*
Response					
Complete response	30	25	26	21	
Partial response	64	54	79	63	
No change	14	12	9	7	
Overall response	94	79	105	84	.315†
95% CI	72-86		78-90		
No. of toxic deaths	3	3	6	5	.346†
Survival					
No. of deaths*	107	90	109	87	
Survival, weeks					.885‡
Median	54		52		
95% CI	47-63		45-61		
Two-year survival		15		18	
95% CI	8-22		11-26		

*Median follow-up: 49 months and 57 months for standard and intensified arm, respectively.
†Stratified Cochran-Mantel-Haenszel test.
‡Stratified log-rank test.

patients (5%) on the intensified arm ($P = .346$). Seven of these nine patients died from an infectious cause, three on the standard and four on the intensified arm, with five being randomized to placebo antibiotics and two to verum antibiotics. In addition, three patients on the standard arm and one patient on the intensified arm died from cardiovascular disease. On both arms, six other patients died from various causes. The median survival time was 54 weeks (95% confidence interval [CI], 47 to 63 weeks) on the standard arm versus 52 weeks (95% CI, 45 to 61 weeks) on the intensified arm ($P = .885$), with 2-year survival rates of 15% and 18%, respectively (Fig 1).

The median progression-free survival was 34 weeks (95% CI, 30 to 38 weeks) on the standard arm versus 31

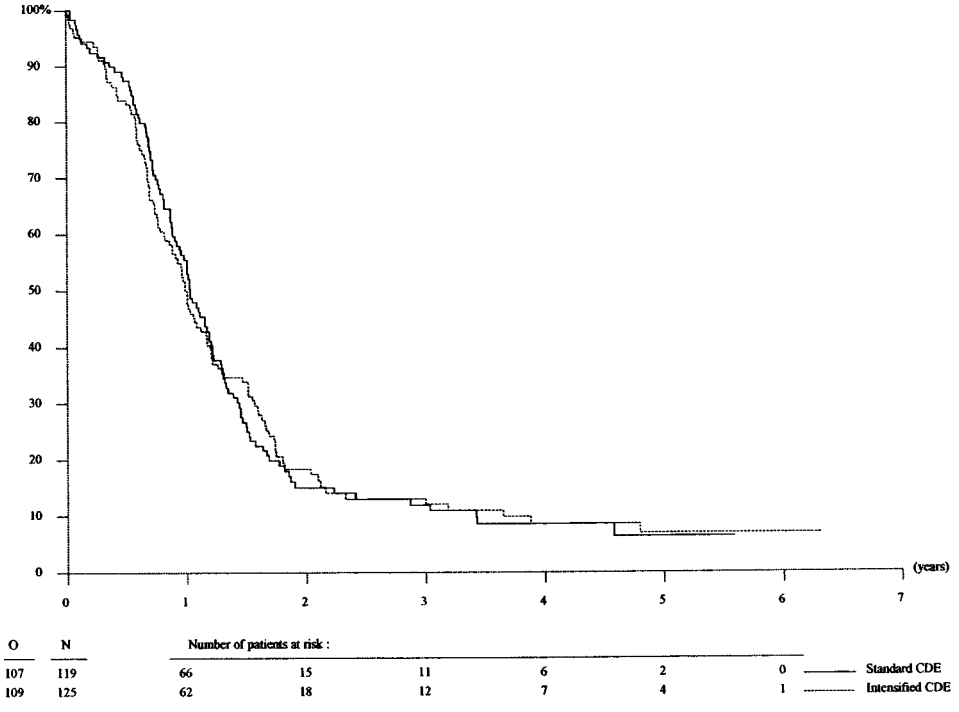

Fig 1. Overall survival by treatment arm.

Table 8. Baseline Prognostic Factors for Survival, All Included in the Cox Proportional Hazards Model

Prognostic Factor	Deaths/No. of Patients	%	Hazard Ratio	95% CI	*P*
Age					
≤ 60 years*	117/134	87	1		
> 60 years	99/110	90	1.181	0.873-1.600	.2807
Weight loss					
≤ 5%*	116/136	85	1		
> 5%	57/61	93	1.407	1.015-1.950	.0406
Disease status					
LD*	114/140	81	1		
ED	102/104	98	2.173	1.588-2.976	< .0001
Performance status					
0*	86/94	92	1		
1	130/150	87	0.884	0.641-1.220	.4546
Antibiotics					
Placebo*	76/80	95	1		
Verum	140/164	85	0.894	0.568-1.406	.6274
Chemotherapy					
Standard*	107/119	90	1		
Intensified	109/125	87	0.740	0.431-1.271	.2794
Interaction					.3883

*Reference category.

weeks (95% CI, 27 to 34 weeks) on the intensified arm ($P = .680$). One- and 2-year progression-free survival rates were, respectively, 24.4% (95% CI, 16.6% to 32.1%) and 8.9% (95% CI, 3.7% to 14.1%) on the standard arm and 21.8% (95% CI, 14.5% to 29.1%) and 11.8% (95% CI, 6.0% to 17.7%) on the intensified arm.

Prognostic Factors for Survival

Factors included in the multivariate Cox proportional hazards model for overall survival were age (≤ 60 *v* > 60 years), weight loss (≤ 5% *v* > 5%), disease status (LD *v* ED), PS (0 *v* 1), antibiotics (placebo *v* verum), chemotherapy regimen (standard *v* intensified), and a term for interaction between chemotherapy and antibiotic treatment (Table 8). The stepdown variable selection procedure removed from this model the antibiotics ($P = .627$), the interaction term ($P = .467$), PS ($P = .550$), the chemotherapy regimen ($P = .539$), age ($P = .311$), and weight loss ($P = .068$). The final multivariate model indicated that having ED was the only prognostic factor for a worse survival (hazard ratio, 2.083; 95% CI, 1.583 to 2.741; $P < .0001$). The median survival time in LD and ED patients was 63 weeks (95% CI, 60 to 77 weeks) and 46 weeks (95% CI, 38 to 46 weeks), respectively. The 2- and 3-year survival rates were, respectively, 26% (95% CI, 18% to 33%) and 19% (95% CI, 12% to 26%) in LD patients and 5% (95% CI, 1% to 10%) and 3% (95% CI, 0% to 7%) in ED patients. After adjustment for extent of disease (LD *v* ED), the effect of dose intensification on survival remained nonsignificant. In fact, in patients with LD, median survival was 62 weeks (95% CI, 50 to 67 weeks) for those treated with standard chemotherapy (59 deaths in 70 patients) versus 77 weeks (95% CI, 61 to 87 weeks) for those treated with intensified chemotherapy (55 deaths in 70 patients) whereas, in patients with ED, the corresponding figures where 51 weeks (95% CI, 36 to 57 weeks) for those treated with standard chemotherapy (48 deaths in 49 patients) versus 40 weeks (95% CI, 36 to 50 weeks) for those treated with intensified chemotherapy (54 deaths in 55 patients).

The fact that the interaction between chemotherapy and antibiotic treatment has not been found to be significant was expected because of the insufficient power to test this interaction. These results seem to confirm that chemotherapy DI is not a prognostic factor for overall survival.

DISCUSSION

This is the first prospective randomized trial assessing the impact of chemotherapy dose intensification obtained by means of both dose size and dose density increase in patients with SCLC. On the experimental arm of this study, planned CDE chemotherapy dose size was 25% higher and chemotherapy dose density was 33% higher, resulting in an overall planned DI increase of nearly 90%, compared with the standard CDE chemotherapy arm. Because of more frequent dose reductions, delays, and omissions on the intensified chemotherapy arm, delivered CDE DI turned out to be actually only 70% higher on this arm compared with the standard CDE arm. Increasing delivered CDE DI by augmenting both dose size and dose density, with the support of prophylactic G-CSF and antibiotics, proved to be

feasible in the context of this multicenter European trial. However, in our study, such a chemotherapy dose intensification did not lead to a significant improvement in either response rate or survival, but led only to an increased hematologic and nonhematologic toxicity.

The sample size of this trial allowed us to detect a 50% difference in median survival with an 80% power. Although a 50% increase in median survival could be regarded as a too-optimistic expectation, the level of planned dose intensification (almost double compared with standard chemotherapy) and the significant increase of toxicity and costs related to growth factors and antibiotic prophylaxis led us to conclude that only a major improvement in survival would have justified the introduction into clinical practice of this experimental regimen.

The role of chemotherapy dose intensification in SCLC has been, so far, controversial. In fact, although retrospective data support a correlation between DI and survival, at least in patients with ED treated with CDE,[16] results of most important prospective randomized trials are inconclusive.

Studies assessing the impact of moderate dose size increase have been generally negative. Ihde et al[5] compared standard cisplatin/etoposide (PE) versus dose-intensified PE with a planned dose size increase of nearly 70% in 90 patients with previously untreated ED SCLC. Although the study had a small sample size, PE dose size intensification did not translate into a significant clinical benefit in that study. Similarly, negative results were also obtained in a Southeastern Cancer Study Group trial of 298 ED SCLC patients assessing the impact of a 20% and a 75% dose size increase of cyclophosphamide and doxorubicin, respectively, within the cyclophosphamide, doxorubicin, and vincristine regimen.[6] Pujol et al[23] sought to assess the impact of a 50% dose size increase of a four-drug chemotherapy regimen including cyclophosphamide, epidoxorubicin, etoposide, and cisplatin in 125 patients with ED SCLC. Surprisingly, patients on the intensified arm had a worse outcome than patients on the standard-dose arm. However, in this study, the role of dose intensification could not be properly assessed because granulocyte-macrophage CSF (GM-CSF) failed to allow the delivery of the planned total dose and dose intensification. The only study showing a significant benefit associated with dose size increase in SCLC is a French trial including 105 patients with LD SCLC where, surprisingly, a 25% increase in chemotherapy dose during the first cycle only led to a statistically significant survival improvement.[7]

The other approach to increase DI, chemotherapy acceleration (also referred to as "dose-dense" chemotherapy), has been more successful. Steward et al[24] assessed the impact of a 25% increase of V-ICE chemotherapy planned DI by reducing the interval between cycles from 4 to 3 weeks, with or without GM-CSF support. Accelerated V-ICE was found to be associated with a statistically significant 25% improvement in median survival. A similar study conducted by the British Medical Research Council yielded the same outcome.[25] On this trial, 403 SCLC patients were randomized between standard CDE recycled at standard 3-week intervals and accelerated CDE recycled every 2 weeks, corresponding to a planned DI increase over the standard of 33%. Also in this study, chemotherapy acceleration was associated with a statistically significant survival improvement. However, the relative gain in 1-year survival with the intensified treatment was only 5%. Conversely, a recently published three-arm study from the European Lung Cancer Working Party, assessing the role of an accelerated epirubicin, vindesine, and ifosfamide regimen with GM-CSF or cotrimoxazole in 233 ED SCLC patients, failed to show any survival improvement associated with dose-dense chemotherapy.[26]

The reason for these contradictory results among studies with a similar design is unclear. A possible confounding factor in our trial, which is the only one using a combination of dose size and dose density increase to achieve maximum chemotherapy DI, might be the use of a 2×2 factorial design in the attempt to answer two different questions at once (ie, impact of DI on survival and impact of antibiotic prophylaxis on FL). The antibiotic part of our study showed a clear benefit in favor of antibiotic prophylaxis in reducing not only FL but also associated complications such as documented infections, hospital admissions, and septic deaths. The benefit of antibiotic prophylaxis was particularly evident in patients receiving dose-intensified chemotherapy.[19] This result suggests a possible interaction between dose intensification and antibiotic prophylaxis, which might have compromised the validity of results achieved in this second part of the trial. However, we have no power to test this possible interaction, and the multivariate analysis performed to assess factors associated with survival outcome indicated a nonsignificant effect of antibiotic prophylaxis as an interaction factor.

In conclusion, increasing CDE DI by nearly 70%, by means of a combination of dose size and dose density increase, did not produce any significant survival benefit compared to conventional dose and schedule. The results of the present study do not allow us to replace full-dose 3-weekly CDE chemotherapy with intensified CDE as the standard regimen for the treatment of SCLC. Given the discrepancy in results from similar studies investigating chemotherapy dose intensification for SCLC, a meta-analysis of all studies so far conducted would be helpful in

further clarifying this issue and in excluding a possible small benefit associated with chemotherapy dose intensification that might be undetectable in the context of a single average-size prospective trial.

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APPENDIX

The appendix listing contributing investigators is available online at www.jco.org.

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