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Original Paper

A Comparison of Methods of Calculation for Estimating Carboplatin AUC with a Retrospective Pharmacokinetic-pharmacodynamic Analysis in Patients with Advanced Non-small Cell Lung Cancer

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We retrospectively analysed the data obtained in a large randomised trial performed in 505 eligible patients with advanced non-small cell lung cancer. Its purpose had been to compare a combination of carboplatin (200 mg/m^2) and cisplatin (60 mg/m^2) with or without the addition of ifosfamide. The present retrospective analysis assessed two ways of dosing carboplatin: according to body surface area (mg/m^2) or to the estimated targeted area under the concentration versus time curve (AUC). Two different methods were used in the latter calculation: the Calvert formula using the Cockroft approximation to evaluate the glomerular filtration rate and the Chatelut equation. There was an excellent linear correlation between them. With the Chatelut method, the calculated administered AUC were lower. Whichever method was used, carboplatin AUC was not significantly associated with antitumour response rate nor patient survival. A statistically significant increase in haematological toxicity, mainly thrombopenia, was observed with an increase in the AUC. This effect was observed whatever AUC variable was considered, i.e. total dosage at course one, total dosage during the first three chemotherapy courses or dose intensity during the first three courses. The effect remained highly significant after adjustment for treatment arm. We conclude that for a moderate carboplatin dose in non-small cell lung cancer, the therapeutic index could be improved if dosage is calculated according to the AUC. **© 1999 Elsevier Science Ltd. All rights reserved.**

Key words: non-small cell lung cancer, chemotherapy, carboplatin, pharmacokinetic, Calvert formula, Chatelut formula
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INTRODUCTION

CARBOPLATIN, A second-generation platinum compound, has a different toxicity profile than cisplatin: nephrotoxicity, neurotoxicity and ototoxicity occur infrequently but myelosuppression, particularly thrombocytopenia, is the dose-limiting toxicity [1]. Its administration has the advantage of not requiring hydration. Thrombocytopenia is more severe in older patients and in those with renal function impairment. Indeed, carboplatin plasma clearance is linearly related to glomerular filtration rate (GFR). Platelet toxicity has been shown by Calvert and colleagues [2] to be more accurately predicted when the dose is calculated on the basis of the patient's renal function and the targeted AUC (area under

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the concentration versus time curve) than when using the traditional method of dosage prescribed according to body surface area. Furthermore, age does not appear to be an independent prognostic factor for carboplatin-induced toxicities when renal function has been taken into account [3]. A series of phase II trials, using the formula developed by Calvert, and many studies with retrospective calculation of the AUC, usually performed with relatively small numbers of patients, are well summarised in a recent review [4]. These have shown that toxicity increases with increasing AUC and that AUC is more closely related to toxicity and efficacy than total dose (mg) or dose based on the body surface area (mg/m^2). The Calvert formula is suitable for a wide range of dosages and it remains accurate if carboplatin is administered in combination with other cytostatic drugs, such as cisplatin or ifosfamide. It must be stressed, however, that to date, there is no published randomised trial comparing the two methods of dosing of carboplatin (AUC versus mg/m^2).

From April 1990 to October 1995, the European Lung Cancer Working Party (ELCWP) performed a large randomised trial comparing, in 505 eligible patients with advanced non-small cell lung cancer (NSCLC), a combination of carboplatin (200 mg/m^2) and cisplatin (60 mg/m^2) with or without the addition of ifosfamide [5]. A standard dosage (mg/m^2) was used for carboplatin, as the Calvert paper had not been published at the time of the study planning. The purpose of this retrospective analysis was to examine the reached AUC and to compare the effect of the two methods of dose calculation on tumour response, survival and toxicity.

PATIENTS AND METHODS

The details of the study have been previously described [5]. Briefly, the eligibility criteria for patients with histologically proven NSCLC were: inoperable stage IV or stage IIIB with pleural effusion; measurable or assessable lesions; no prior history of malignancy except non-melanoma skin cancer, *in situ* carcinoma of the cervix or 'cured' malignant tumour (more than 5-year disease-free survival); no prior chemotherapy; age < 75 years; Karnofsky performance status (PS) > 60; good renal (serum creatinine level < 1.3 mg/dl and/or creatinine clearance > 60 ml/min), hepatic (serum bilirubin level < 1.5 mg/dl) and haematological white blood cell (WBC) count > 4000/μl and platelet count > 100 000/μl) functions; no recent (less than 3 months before the date of treatment) myocardial infarction and no active congestive heart failure or cardiac arrhythmia requiring medical treatment; no uncontrolled infectious disease. Patients had to be accessible for follow-up and to have provided informed consent.

Eligible patients were randomised between two arms: the CC regimen consisting of moderate doses of a combination of cisplatin (30 mg/m^2 on days 2 and 3) plus carboplatin (200 mg/m^2 on day 1) and the CCI regimen consisting of the CC combination plus ifosfamide (1.5 g/m^2 on days 1, 2 and 3). Carboplatin was administered on day 1, intravenously (i.v.) in 250 ml 5% dextrose over 30 min, followed by 2000 ml NaCl 0.9% with 3 g KCl over 24 h. If urine output decreased to < 400 ml per 6 h, i.v. furosemide (20 mg) was administered. Cisplatin (30 mg/m^2) was given on days 2 and 3 i.v. over 15 min in 250 ml NaCl 0.9%, followed by a posthydration with 3000 ml of 5% dextrose in NaCl 0.45% with 1.5 g KCl/l over 24 h. If urine output decreased to < 500 ml per 6 h, i.v. furosemide (20 mg) was administered. Ifosfamide was administered in 1 l of NaCl 0.9% over 3 h, just after cisplatin or carboplatin, with i.v. mesna at a dose of 300 mg/m^2 just before ifosfamide and then every 4 h for 72 h. To control emesis, the administration of a 5-HT$_3$ antagonist, tropisetron (kindly provided by the Sandoz Company, Basle, Switzerland), was recommended with the following schedule: 5 mg orally the evening preceding chemotherapy administration, 5 mg as a slow i.v. infusion before administration of chemotherapy and 5 mg orally per day 1 h before breakfast for 4 additional days after the start of chemotherapy.

Courses were repeated every 3–4 weeks, according to haematological status. If treatment had to be postponed after day 35 of the last treatment, the patient was removed from the study. Tumour response was assessed after three full courses. In the case of stable disease, patients received three further courses. In the case of progression, the treatment was discontinued. Responding patients were administered additional courses until best response, progression or major toxicity.

In both arms, subsequent cisplatin was administered at 50% of the initial dose if the serum creatinine increased above 1.5 mg/dl. It was discontinued if it increased beyond 3 mg/dl, even if it returned to normal values. In the case of myelotoxicity, treatment was postponed until the WBC count increased to > 4000 /μl and platelets to > 100 000/μl. If the WBC nadir was < 1000/μl and/or the platelet nadir was < 100 000/μl, carboplatin and ifosfamide were reduced to 75% of the initial dosage. In the case of WHO grade III or more neurotoxicity or clinical evidence of hearing loss, cisplatin was stopped.

The initial work-up and those performed at restaging and during follow-up as well as the criteria for response, duration of response, survival and toxicity and the randomisation procedure have been previously published [5, 6].

The influence of the modality of prescription of carboplatin according to body surface area or to carboplatin clearance related to the renal function was evaluated according to the Calvert AUC-based equation [2]; glomeruler filtration rate (GFR) was evaluated according to the Cockroft formula [7] from the serum creatinine level that was measured before each new cycle of chemotherapy; and carboplatin clearance according to weight, age, sex and serum creatinine was calculated using the Chatelut formula [8]. The equations are shown in Table 1.

The association between delivered AUC dose categories and response or haematological toxicity was analysed with contingency tables. Survival curves were estimated by the method of Kaplan and Meier [9]. The log-rank test was used to compare survival curves [10]. *P* values for testing differences between proportions were calculated with chi-square tests or with Fisher's exact tests. A multivariate analysis for comparison adjustment taking into account prognostic factors was performed by fitting the data with a Cox model for duration of survival and a logistic model for objective response [11, 12].

Calculating absolute and relative dose intensities assessed chemotherapy intensity. The absolute dose intensity was defined as the ratio of the received dose per body surface area to the actual duration of treatment: it was expressed in mg/m^2/week. The relative dose intensity was defined, for each drug, as the ratio of the received dose divided by the scheduled dose to the actual duration of treatment divided by the scheduled duration. The total relative dose intensity is the mean of the relative dose intensities of all the drugs. These formulae have been previously published [13].

RESULTS

The results of the study have been published previously [5, 6], but patient characteristics and the main results are detailed in Tables 2 and 3. The median follow-up duration was 155 weeks, ranging from 2 to 235 weeks. At the time of analysis, 460 patients were dead, 35 were alive and 10 were lost to follow-up. There was a 16% objective response rate to CC (15% of the eligible patients) and a 31% objective response rate to CCI (28% of the eligible patients). This difference was statistically highly significant ($P < 0.001$). Duration of response and survival were not statistically different between the two arms. Main toxicity consisted of emesis, alopecia, leucopenia and thrombopenia. Those side-effects were significantly more frequent and more severe in the CCI arm. Chronic auditive, renal or peripheral neurological toxicity was infrequent and not significantly increased by the addition of ifosfamide. Dose intensity was significantly reduced in the CCI arm, with an average relative dose intensity of 76.1% in comparison with 87.5% for the CC arm ($P < 0.0001$).

Calculating the carboplatin dosage according to the Calvert–Cockroft and Chatelut methods (Table 1) assessed the potential influence of the mode of prescription of carboplatin. 9 of the 505 eligible patients were excluded from this analysis because data needed in the calculations were missing ($n = 3$) or because treatment was never administered ($n = 6$, 3 per arm). During the first course of chemotherapy, mean ± standard deviation (S.D.) AUC were, respectively, 3.34 ± 0.8 for the CC regimen and 3.46 ± 0.7 for the CCI regimen with the Calvert–Cockcroft formula. With the Chatelut approximation for the calculation of creatinine clearance, the corresponding mean S.D. AUC were 2.65 ± 0.7 and 2.74 ± 0.7. There was no difference between the two arms. The linear correlation between the doses calculated by the two methods was excellent ($r = 0.91$). For the analysis, we divided the eligible patients into three groups according to the AUC administered during the first treatment course. Using the Calvert–Cockcroft method, they were divided as follows: AUC < 3, 137 patients; AUC 3–4, 260 patients; AUC > 4, 99 patients. With the Chatelut method, they were divided as: AUC < 2.5, 203 patients; AUC 2.5–3.5, 151 patients; AUC > 3.5; 142 patients.

The relationship between AUC dose and tumour response is detailed in Table 4. Whichever method was used to calculate the AUC and whether assessed continuously or categorised into three classes, there was no significant association between the carboplatin AUC dosage administered and the objective response rate. Bivariate regression logistic models were used for treatment effect adjustment with three variables related to the carboplatin AUC administered: received AUC at cycle 1, cumulative AUC dose after the first three courses of chemotherapy, AUC dose intensity delivered during the first three cycles. In no instance was there an impact of the AUC variable on the objective response rate, whilst the treatment arm had a significant impact in each situation with an increased objective response rate by the CCI regimen.

The impact of AUC carboplatin dosage on survival was evaluated according to the AUC delivered at the first cycle or to the cumulative AUC administered after the first three courses of chemotherapy. There was no difference between

Table 1. Calvert's formula and equations for glomeruler filtration rate estimation (GFR)

Calvert's formula

$$\text{Carboplatin dosage} = \text{AUC} \times (\text{GFR} + 25)$$

Dosage: mg
AUC: mg×min/ml
GFR: ml/min, estimated by the Cockcroft method.

$$\text{GFR} = \frac{1.23 \times (140 - \text{age}) \times \text{weight} \times \text{sex}}{\text{Serum creatinine}}$$

Age: years
Weight: kg
Serum creatinine: μM concentration
Sex: 1 for a male, 0.85 for a female

Chatelut's method

$$\text{Carboplatin dosage} = \frac{\text{Carboplatin clearance}}{\text{AUC}}$$

Dosage: mg
Carboplatin clearance: ml/min

$$\text{Carboplatin clearance} = 0.134 \times \text{weight} + \frac{[218 \times \text{weight} \times (1 - 0.00457 \times \text{age}) \times (1 - 0.314 \times \text{sex})]}{\text{Serum creatinine}}$$

Weight: kg
Age: years
Sex: 0 for a male, 1 for a female
Serum creatinine: μM concentration

AUC, area under the concentration versus time curve.

Table 2. Patient characteristics [5]

Characteristic	Treatment arm CC	CCI
Number of eligible patients	248 (5)	257 (4)
Sex male/female	212/36 (4/1)	227/30 (4/–)
Median age (range) (years)	60 (35–75)	61 (32–75)
PS (Karnofsky)		
< 70	86 (4)	83 (1)
> 80	162 (1)	174 (3)
Types of lesions		
Assessable	120 (3)	150 (4)
Measurable	128 (2)	107
Disease extent		
Stage IIIB	13	10
Stage IV	235 (5)	247 (4)
Histology		
Squamous cell carcinoma	107 (2)	89 (4)
Adenocarcinoma	100 (2)	112
Large cell carcinoma	20 (1)	29
Other non-small cell	21	27
Prior chest irradiation	12	14
Loss of body weight		
< 5%	109	112 (1)
> 5%	91 (3)	93 (3)
Unknown	48 (2)	52
Number of metastatic sites		
0	13	10
1	67	67 (1)
2	97 (5)	112 (1)
3	48	42 (1)
4	16	23 (1)
> 5	7	3
Patients with brain metastases	61 (1)	69 (1)

Patients not eligible for the present retrospective analysis are in parentheses. CC, cisplatin plus carboplatin; CCI, CC plus ifosfamide; PS, performance status.

Table 3. Summary of the results of the randomised comparison between cisplatin plus carboplatin (CC) and CC plus ifosfamide (CCI) [5]

	CC	CCI	*P*
Number of eligible patients	248	257	
Number of patients assessable	220	238	
Objective response rate	35 (16%)	74 (31%)	< 0.001
Median duration of response	28 weeks	30 weeks	NS
Median survival time	27 weeks	27 weeks	NS
1-year survival rate	23%	26%	
2-year survival rate	5%	6%	
Haematological toxicity (first three courses)			
Leucopenia			
Grade I–II	33%	43%	
Grade III–IV	7%	28%	< 0.00001
Thrombopenia			
Grade I–II	21%	46%	
Grade III–IV	12%	30%	< 0.00001
Relative average dose intensity (first three courses)	87.5%	76.1%	< 0.0001

CC, cisplatin plus carboplatin; CCI, CC plus ifosfamide; NS, not statistically significant.

the three AUC groups. The results were similar when AUC was calculated by the Chatelut method. Cox regression models were applied with adjustment for the treatment arm (CC versus CCI). They failed to show any effect of the AUC dose (with both methods) on survival, whether AUC at course 1, cumulative AUC given during the first three courses or dose intensity in AUC after three courses was considered.

Haematological toxicity appeared to be significantly associated with the carboplatin AUC dose delivered. Tables 5 and 6 show the results, respectively, for the association with leucopenia and thrombopenia. The effects were more severe for thrombocytopenia.

The occurrence of grade III–IV thrombocytopenia appeared to be highly related to the carboplatin AUC dose (Table 6). Using the Calvert–Cockcroft formula, the risk was 6% for an AUC ≤ 3, 10% for an AUC between 3 and 4 and 20% for an AUC > 4 given at course 1 (test for linear association: $P = 0.002$). With the Chatelut method, it was 6% for an AUC ≤ 2.5, 9% for an AUC between 2.5 and 3 and 20% for an AUC > 3 (test for linear association: $P < 0.001$). The effect remained highly significant after adjustment for treatment arm in a logistic regression model. With the Calvert–Cockcroft method, the odds ratio (OR) for increased toxicity was 2.90 ($P = 0.003$) in favour of the CC arm and 2.04 ($P = 0.001$) in favour of low carboplatin AUC. With the Chatelut method, the OR was 2.90 ($P = 0.003$) for the treatment arm and 2.19 ($P < 0.001$) for the AUC dose. The risk was highly associated with the cumulative AUC dose delivered after the first three courses as shown in Table 6. It remained highly significant after adjustment for treatment in a logistic regression model. With the Calvert–Cockcroft method, the OR were, respectively, for treatment arm and AUC dose, 4.01 ($P = 0.0001$) and 1.41 ($P < 0.0001$). With the Chatelut formula, they were, respectively, 3.98 ($P = 0.001$) and 1.45 ($P < 0.001$). Similar results were obtained when the dose intensity in AUC after three courses was considered (Table 2) with persistence of the significant effect after adjustment for treatment arm in a logistic regression model. In that model, with the Calvert–Cockcroft method, the respective OR for treatment arm and AUC dose were 3.92 ($P = 0.0001$) and 1.21 ($P = 0.006$). With the Chatelut formula, they were 3.92 ($P = 0.001$) and 1.27 ($P = 0.003$).

DISCUSSION

Our retrospective study shows that in a series of patients with advanced NSCLC treated with a chemotherapy regimen including moderate carboplatin dose, the therapeutic index is improved when the drug dosage is calculated according to the AUC, in comparison with the traditional method of using body surface area. This approach is associated with decreased

Table 4. Relationship between carboplatin AUC dose and antitumour response

	Cockcroft–Calvert method			Chatelut method		
	AUC	Response rate (%)	*P*	AUC	Response rate (%)	*P*
Delivered dosage at course 1 ($n = 456$)	≤ 3	30/124 (24)		≤ 2.5	49/184 (27)	
	3–≤ 4	58/240 (24)		2.5–≤ 3	33/141 (23)	
	> 4	21/92 (23)	NS	> 3	27/131 (21)	NS
Delivered cumulative dosage during the first three courses ($n = 300$)	≤ 9	28/105 (27)		≤ 7.5	43/136 (32)	
	9–≤ 12	46/139 (33)		7.5–≤ 9	29/89 (33)	
	> 12	21/56 (38)	NS	> 9	23/75 (31)	NS
Dose intensity administered during the first three courses ($n = 300$)	≤ 9	63/189 (33)		≤ 7.5	68/209 (33)	
	9–≤ 12	28/98 (29)		7.5–≤ 9	19/59 (32)	
	> 12	4/13 (31)	NS	> 0	8/32 (25)	NS

AUC, area under the concentration versus time curve; NS, not significant.

Table 5. *Relationship between carboplatin AUC dose and leucocyte toxicity*

	Cockcroft–Calvert method			Chatelut method		
	AUC	Grade III–IV toxicity (%)	*P*⋆	AUC	Grade III–IV toxicity (%)	*P*⋆
Delivered dosage	≤ 3	11/119 (9)		≤ 2.5	18/174 (10)	
at course 1 ($n = 421$)	3–≤ 4	39/211 (18)		≤ 2.5–≤ 3	25/124 (20)	
	> 4	23/91 (25)	0.001	> 3	30/123 (24)	0.001
Delivered cumulative dosage	≤ 9	18/105 (17)		≤ 7.5	26/131 (20)	
for the first three courses ($n = 295$)	9–≤ 12	38/134 (28)		7.5–≤ 9	22/89 (25)	
	> 12	20/56 (36)	0.01	> 9	28/75 (37)	0.01
Dose intensity administered	≤ 9	47/187 (25)		≤ 7.5	53/203 (26)	
during the first three courses ($n = 295$)	9–≤ 12	27/95 (28)		7.5–≤ 9	12/60 (20)	
	> 12	2/13 (15)	NS	> 9	11/32 (34)	NS

⋆Test for linear association. AUC, area under the concentration versus time curve; NS, not significant.

haematological toxicity and similar antitumour activity in terms of response rate and survival. To our knowledge, this series is the first large retrospective analysis of this topic in lung cancer patients and it confirms the findings of a study of 1028 ovarian cancer patients [3]. That study, the largest one performed on the topic, showed that carboplatin dosing by AUC led to more predictable toxicity [3].

Contrary to the ovarian cancer study, we failed to demonstrate a relationship between AUC dosage and antitumour response. This might be explained by the low doses of carboplatin administered to our patients with a delivered AUC usually between 2 and 4 and by the fact that NSCLC is less sensitive to carboplatin than ovarian cancer. Moreover, our patients also received cisplatin and/or ifosfamide which we consider to be more active against lung cancer. In the ovarian cancer study, patients were treated with single-agent carboplatin therapy. A criticism might be that cisplatin and ifosfamide are known to be nephrotoxic. They could thus have had an effect on carboplatin clearance. The studies by Calvert–Cockroft and Chatelut were performed on patients who were not receiving cisplatin and the impact of ifosfamide on creatinine-based estimations of carboplatin clearance has so far not been investigated. Further investigations will be necessary to rule out a potential interfering effect.

A limitation of our study was its retrospective nature, a criticism that also applies to the other studies performed on this topic. To date, no published randomised trial has evaluated in a given tumour the dosing of carboplatin according to AUC versus body surface area. The usage of AUC for carboplatin dosing is based on retrospective analyses and small prospective trials with historical comparisons. A problem of the retrospective nature of the present study was the presence of missing data leading to the exclusion of patients from the analysis. As this exclusion rate was less than 2% of the overall population, it is very improbable that this could be a significant bias interfering with response and survival analyses. However, the exclusion rate was greater (17%) for the study of the impact on toxicity of the delivered dosage at course 1: a potential bias can probably be eliminated because the analysis of the delivered cumulative dosage during the first three courses provided similar results with very few exclusions (< 2%).

Carboplatin clearance is directly related to creatinine clearance. As we did not have a direct measurement of this last parameter, we extrapolated its level from serum creatinine using the Cockcroft approximation [7]. We also used a formula other than the Calvert equation [2], the Chatelut method, which appeared to better predict carboplatin clearance [8]. The strong linear relationship observed between both methods can be explained by the fact that they use three similar patient variables (creatinine, age, weight). The Calvert–Cockcroft formula provided, for a given patient, an AUC superior to the Chatelut formula, an observation already described by Paccagnella and colleagues in NSCLC [14]. This difference might be explained by the fact that the Cockcroft formula tends to underestimate GFR [15]. However, the results in terms of impact of the AUC on response rate, survival and toxicity were very similar. It is very important from a practical and prospective point of view to calculate the carboplatin dose using only one of the aforementioned

Table 6. *Relationship between Carboplatin AUC dose and platelet toxicity*

	Cockcroft–Calvert method			Chatelut method		
	AUC	Grade III–IV toxicity (%)	*P*⋆	AUC	Grade III–IV toxicity (%)	*P*⋆
Delivered dosage	≤ 3	7/119 (6)		≤ 2.5	11/174 (6)	
at course 1 ($n = 421$)	3–≤ 4	21/211 (10)		2.5–≤ 3	11/124 (9)	
	> 4	18/91 (20)	0.002	> 3	24/123 (20)	< 0.001
Delivered cumulative dosage	≤ 7.5	10/105 (10)		≤ 9	16/131 (12)	
for the first three courses ($n = 295$)	7.5–≤ 9	28/134 (21)		9–≤ 12	16/89 (18)	
	≥ 9	22/56 (39)	< 0.001	> 12	28/75 (37)	< 0.001
Dose intensity administered	≤ 7.5	31/187 (17)		≤ 9	32/203 (16)	
during the first courses three ($n = 295$)	7.5–≤ 9	23/95 (24)		7.5–≤ 12	15/60 (25)	
	> 9	6/13 (46)	0.009	> 12	13/32 (41)	< 0.001

⋆Test for linear association. AUC, area under the concentration versus time curve.

methods for a given protocol and to define precisely the method used. A more direct measurement of the GFR, for example by Cr^{51} EDTA clearance, provides more accurate dosing [16] but is not very practicable [17], as the test needs to be repeated before each new chemotherapy course. Dosage directly based on carboplatin plasma concentration measurement after a test dose could perhaps become a more appropriate way to administer carboplatin [18, 19], but this requires appropriate validation.

In conclusion, this retrospective study shows that, the carboplatin dosage according to body surface area is not appropriate in patients with NSCLC because it produces very variable haematological toxicity due to the fact that carboplatin renal clearance is not taken into consideration. The traditional method of individualising cytotoxic drug dose by using body surface area, a method of the past that is probably not valid for all drugs [20–22], can be detrimental in the case of carboplatin. A more appropriate method is the prescription of a targeted AUC using the Calvert or Chatelut equations.

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APPENDIX
PARTICIPATING INSTITUTIONS (WITH INVESTIGATORS)

Intitut Jules Bordet, Brussels, Belgium (J.P. Sculier, M. Paesmans, P. Mommen, P. Van Houtte, J. Klastersky). Hôpital Civil de Charleroi, Charleroi, Belgium (J. Thiriaux, J. Lecomte). Groupe Médical Saint-Remi, Reims, France (G. Bureau, J.M. Faupin, J. Jouet, F. Masure). Hospital Malva Rosa, Valencia, Spain (V. Giner). Hellenic Cancer Institute, Athens, Greece (A. Efremidis, G. Koumakis). Hôpital Albert Calmette, Lille, France (J.J. Lafitte). Hôpital d'Hayange, Hayange, France (M.C. Berchier). Evangelismos General Hospital, Athens, Greece (C.G. Alexopoulos, M. Vaslamatzis). C.H.I. de Montfermeil, Montfermeil, France (C. Zacharias). Hôpital Saint-Pierre, Brussels, Belgium (V. Ninane, R Sergysels). Hôpital de Warquignies, Boussu, Belgium (P. Libert, M. Richez). C.H. de Douai, Douai, France (M.C. Florin, E. Maetz, A. Strecker). Hôpital Brugmann, Brussels, Belgium (J. Schmerber). IMC Mutualités Socialistes, Tournai, Belgium (A. Tagnon, G. Nuttin). Clinique de La Louvière, Lille, France (F. Fortin, J.M. Dernis, J.M. Grosbois). C.H. de Roubaix, Roubaix, France (F. Kroll, F. Steenhouwer). Klinika radiotherapie a onkologie, Kosice, Slovakia (J. Baumöhl). Hôpital Ambroise Paré, Mons, Belgium (P. Recloux). Clinique Louis Caty, Baudour, Belgium (V. Richard, D. Diana). C.H.U. A. Vésale, Montigny-le-Tilleul, Belgium (D. Brohée). C.H.U. de Nantes, Nantes, France (G. Dabouis). Clinique Saint-Luc, Namur, Belgium (O. Van Cutsem, M. Mairesse). Hôpital de Braine-l'Alleud, Braine-l'Alleud, Belgium (C. Finet). Hôpital de la Madeleine, Ath, Belgium (P. Ravez). Clinique des 2 Alice, Brussels, Belgium (R. Cordier). C.H. de Luxembourg, Luxemburg (F. Ries). Research Institute of Tuberculosis and Respiratory Disease, Prague, Czech Republic (P. Opalka). Centre Hospitalier Paul Brien, Brussels, Belgium (C. Cauchie). Hôpital Duchenne, Boulogne sur Mer, France (J.L. Crépin). C.H. Peltzer-La Tourelle, Verviers, Belgium (J.L. Corhay). Institut Edith Cavell, Brussels, Belgium (C. Van Haelen). Höpital du CPAS de Soignies, Soignies, Belgium (M. Denaut).