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Outcome is not improved by the use of alternating chemotherapy in elderly patients with aggressive lymphoma

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Introduction: A prospective randomised study involving 810 elderly patients was conducted in an attempt to compare alternating chemotherapy with conventional first-line chemotherapy in aggressive non-Hodgkin's lymphoma in order to improve prognosis with an acceptable toxicity for elderly patients.

Patients and methods: Patients included were 55–69 years old and had at least one adverse prognostic factor. Patients were treated either with ACVBP followed by consolidation ($n=396$) or with an alternating regimen ($n=414$). This regimen was an association of active drugs in NHL relapsing patients, alternating VIMMM with ACVBP for induction and alternation of VIM and ACVM in consolidation. Eight hundred and sixty-six patients were randomised. After histological review, 810 patients met the inclusion criteria: 396 in arm A, 414 in arm B.

Results: The complete response rate after induction was superior for conventional first-line therapy (58.5% *vs* 48%, $P=0.003$) but at the end of treatment, the CR rate was not statistically different (52% *vs* 48%, $P=0.19$). Conventional chemotherapy had a better five-year event-free survival than alternating regimen (33% (95% CI: 30–36%) *vs* 28% (95% CI: 26–30%), $P=0.0289$) but overall survival was not statistically different (40% (CI 95% 38–42%) *vs* 36% (CI 95% 34–38%), $P=0.068$). In this elderly high risk population. the toxicity was very high: 19% in arm A and 26% in arm B died during treatment.

Conclusion: Alternating regimen did not improve outcome, was less efficient and more toxic. *The Hematology Journal* (2001) **2**, 279–285

Keywords: aggressive lymphoma; elderly; alternating chemotherapy

Introduction

The treatment of aggressive lymphoma patients has been considerably improved by the use of combination chemotherapy. The CHOP regimen has become the standard regimen, leading to 30–40% long-term survival without difference in efficacy compared with other regimens.[1] On the other hand, high-dose CHOP regimen (ACVBP regimen) such as developed by the multi-centre French-Belgian Study Group for Adult Lymphoma (Groupe d'Etudes des Lymphomes de l'Adulte GELA) made for 50% long-term survival.[2]

However, the outcome in aggressive lymphoma depends on the presence of adverse prognostic factors, as defined by the International Non-Hodgkin's Lymphoma Prognostic Factors Project (IPI).[3] Five-year survival varies from 73% for low-risk to 26% for high-risk patients. Therefore suitable strategies must be chosen according to risk factors and more aggressive treatments have to be developed for patients with the poorest outcomes.

Because growth factors were not available in 1987, the population of patients aged 55–70 years did not receive myeloablative therapy and transplantation. Nevertheless, they were able to receive more aggressive treatment than the conventional regimen. One of the options was to introduce an alternating therapy, such as that defined by a mathematical model[4] that predicts the occurrence of mutations depending on the type of tumour, and predominantly tumour size. According to

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this assumption, clones resistant to chemotherapy are present before the beginning of treatment; thus, to overcome clinical resistance, a maximum of different drugs must be combined. Alternating non-cross-resistant chemotherapy is one possibility for combining drugs and preventing the development of resistant tumour cell clones.[5] A variety of combination regimens such as MACOP-B, ProMACE-MOPP and ProMACE CytaBOM have been developed in accordance with this theory.[6,7]

To test this hypothesis the LNH84 regimen based on ACVBP induction and low-toxicity sequential chemotherapy in consolidation,[8] was compared with a new alternating regimen involving VIMMM and ACVBP (see Treatment section) in induction, followed by VIM alternating with ACM in consolidation. New drugs were chosen because of their efficacy in salvage regimens: ifosfamide, VP16 or VM26, Methyl-GAG, methotrexate and mitoxantrone.[9–11]

In this prospective study, we treated patients between 55 and 70 years of age with aggressive lymphoma and at least one adverse prognostic factor defined in 1987 (before IPI): poor performance status, high number of extranodal sites, large tumour, bone-marrow (BM) or central nervous system (CNS) involvement, Burkitt or lymphoblastic histology.

The main objective was to improve overall survival. The secondary objectives were to increase the complete response rate and the time to treatment failure in this sub-population with aggressive lymphoma, which includes patients who are unable to receive intensive chemotherapy and autologous stem cell transplantation.

Patients and methods

Eligibility criteria

A prospective, randomised phase III trial with 34 participating centres in France and five in Belgium (see Appendix) was initiated in October 1987 and closed in March 1993.

Study eligibility requirements were newly diagnosed patients aged between 55 and 69 years with intermediate- or high-grade non-Hodgkin's lymphoma according to the Working Formulation[12] and the presence of at least one of the following adverse factors: Eastern Cooperative Oncology Group (ECOG)[13] performance status >1; more than one extranodal site; tumour burden $\geqslant 10$ cm in the largest dimension; BM or CNS involvement; and Burkitt's or lymphoblastic subtypes without BM or CNS involvement. Patients were not included in the study if they had a positive serology to human immunodeficiency virus; a concomitant or previous cancer (except *in situ* cervical carcinoma or skin epithelioma); congestive heart failure; recent myocardial infarction or conduction abnormalities; uncontrolled diabetes mellitus; or liver/kidney failure not related to the lymphoma. This study protocol was approved by the institutional ethics committee and patients gave written informed consent.

Staging procedure

The staging procedure included a complete physical examination, routine blood chemistry analyses, thoracic X-ray, and computed tomographic (CT) scans of the thorax and abdomen. All patients had a bone-marrow biopsy. Other staging procedures were performed depending on clinical requirements. The number of extranodal sites and the diameter of the largest tumour mass were determined. Patients were staged according to the Ann Arbor system.[14]

Performance status was based on the ECOG Scale (0–4).[13] Serum lactate dehydrogenase (LDH) levels were expressed as a percentage of the maximum normal value. β_2 microglobulin level was expressed in mg/l.

Responses were carefully evaluated for all parameters that had been abnormal before therapy. Responses were evaluated after induction and at the end of the treatment.

Histological and immunophenotypic analysis

Histological review by three independent GELA hematopathologists was performed and used for analysis in 83% of patients. The diagnosis of the local pathologist was used for the remaining 17% of patients. The Ki-1$^+$ anaplastic large-cell subtype was added to the categories of the Working Formulation.

Immunophenotypic studies were performed on deparaffinised tissue sections, using a panel of antibodies directed against B- (CD20/L26, CDw75/LN1, MB2) and T- (CD3, CD45Ro/UCHL1) cell-associated antigens.

Treatment

A schema of the study is provided in Figure 1. The LNH84 protocol used in this trial has already been described.[8] Briefly, it consists of four courses of ACVBP (Adriamycin 75 mg/m^2 day 1; Cyclophosphamide 1200 mg/m^2 day 1; Vindesine 2 mg/m^2 day 1,5; Bleomycine 10 mg day 1,5; Prednisone 60 mg/m^2 days 1–5) given at three-weeks intervals followed by consolidation with high-dose methotrexate (3000 mg/m^2 × 2), ifosfamide (1500 mg/m^2 × 2), VP16 (150 mg/m^2 × 2), L-asparaginase (5000 ui/m^2 × 2) and Ara-C (100 mg/m^2 × 8).

The alternating regimen consisted of two cycles of chemotherapy VIMMM (VM26 (teniposide) 100 mg/m^2 administered intravenously (i.v.) on days 1 and 5; Ifosfamide 1000 mg/m^2 i.v. on days 1–3; Mitoxantrone 10 mg/m^2 i.v. on day 1; Methylgag 300 mg/m^2 i.v. on days 1 and 5; Methotrexate 1500 mg/m^2 i.v. on day 14; Methylprednisone 60 mg/m^2 given orally on days 1–5) alternating with two ACVBP cycles in induction. During consolidation, patients received 2 cycles of VIM (VP16 (etoposide) 150 mg/m^2 i.v. on days 1–3;

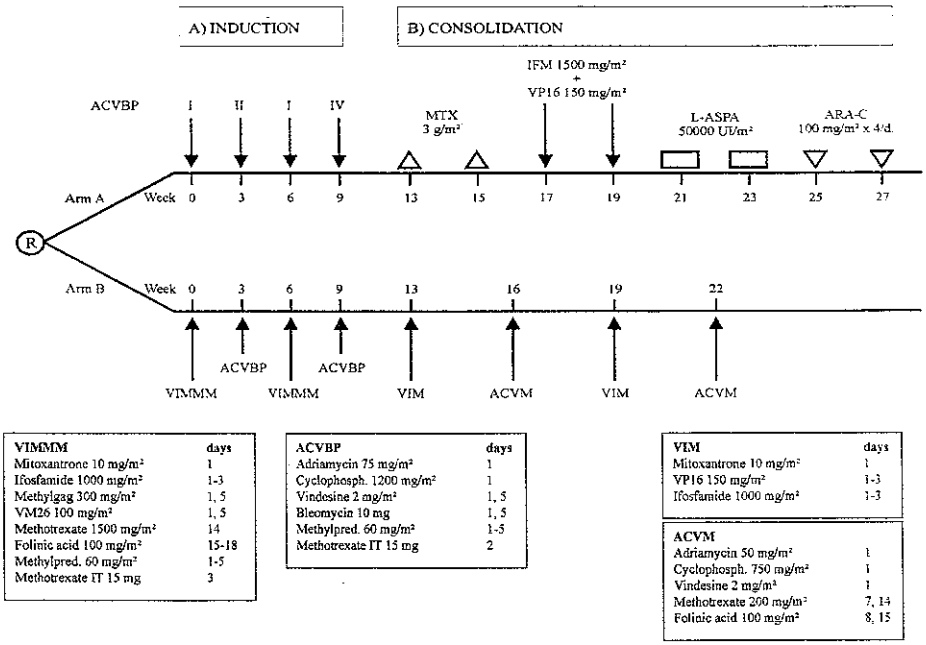

Figure 1 Outline of the study. Arm A is the reference arm (ACVBP+consolidation). Arm B is the experimental arm alternating chemotherapy.

Ifosfamide 1 g/m² i.v. on days 1–3; Mitoxantrone 10 mg/m² i.v. on day 1) alternating with two ACVM cycles (Adriamycin 50 mg/m² i.v. on day 1; Cyclophosphamide 750 mg/m² i.v. on day 1; Vindesine 2 mg/m² i.v. on day 1; Methotrexate 200 mg/m² administered i.v. on days 7 and 14).

No chemotherapy dose-reduction was allowed and the time between cycles was extended in the case of neutropenia.

Patients did not receive any growth factor except for 116 patients included in a double-blind multi-centre phase III trial of rGCSF (Filgrastim) *vs* placebo: 57 patients received Filgrastim.

Statistical methods

Randomisation was stratified according to participating centres. The randomisation sequence was generated by the GELA Cooperative Studies Programme Coordinating Centre, which issued treatment allocation by telephone after confirmation of patient eligibility. The primary objective of the study was to detect a 15% difference in survival between the two treatment arms on the basis of a 30% projected three-year survival period in the LNH84 arm with an α risk = 0.05 and a β risk = 0.1. Secondary objectives included assessment of response to induction, event-free survival and toxicity. Information collected at participating centres was sent to the Coordinating Centre for management and review. All information was checked routinely for outliers and erroneous values.

Complete response (CR) was defined as the disappearance of all clinically measurable disease for at least one month and partial response (PR) as a reduction of more than 50% of all measurable disease. Uncertain CR (CRu) was defined as PR >75% with no evidence of residual mass activity.

Overall survival (OS) was measured from the date of randomisation to the date of death, a last observation or stopping date. Event-free survival (EFS) was calculated from the date of randomisation for all patients to relapse, disease progression, death, date of last observation, or stopping date. Survival curves were calculated using the Kaplan-Meier method.[16]

All analyses were performed on an intention-to-treat basis. The stopping date was set as 30 July 1998. Patient characteristics, frequency of adverse reactions and effect of prognostic factors on CR rate were analysed using χ^2 test and logistic regression. Survival rates (EFS and OS) were analysed using the log rank test. The Kaplan Meier plot of time to first event was also produced.[16]

The Cox proportional hazard model was used after adjustment to the baseline parameters.[17] Concerning regression and Cox model, the results are presented in terms of the odds-ratio for the co-variates effect, the 95% confidence limits for the odds-ratio and associated probability values. The nominal significance level for the end-points was set to 0.05 (two-sided test).

Results

A total of 866 patients entered the trial between October 1987 and March 1993. After histological re-examination, patients ($n=56$) with follicular lymphomas ($n=26$), small diffuse lymphocytic lymphomas

($n=20$), carcinomas ($n=4$), Burkitt's lymphomas with BM involvement ($n=3$), Hodgkin's disease ($n=3$) were excluded. Thus, remaining patients ($n=810$) met the inclusion criteria and were randomised for treatment with the LNH84 regimen (Arm A; $n=395$) or with the alternating treatment as described above (Arm B; $n=415$). Median follow-up time was 80 months.

Characteristics

The mean age of patients in both arms was 62 years (Table 1). Two patients <55 years were included in Arm A and one patient who was 70 years old was included in Arm B. No statistical differences were observed in the characteristics of patients in the two treatments groups. Patients had several adverse prognosis factors including age >60 years (63%); tumour size ⩾10 cm (51%); high LDH level (64%); advanced disease stage (80%); poor performance status (38%); two or more extranodal sites (47%): CNS involvement (11%); BM involvement (37%); high β_2 microglobulin level (49%): low serum albumin (24%); and B symptoms (57%). According to the IPI classification, 13% had a low risk (0–1 factor), 25% a low intermediate risk (2 factors), 33% a high intermediate risk (3 factors) and 28% a high risk (4–5 factors).

Table 1 Characteristics of the 810 patients: percentage of the cases. None of these characteristics shows significant differences between the two arms

	Arm A ($n=395$)	*Arm B* ($n=415$)
Age mean (min–max)	62 years (53–70)	62 years (37–69)
⩽60	37	38
>60	63	62
Sex		
Male	55	53
Female	45	47
Immuno		
T	16	15
B	84	85
Histology		
D	4	3
E	3	2
F	9	11
G	55	56
H	14	13
I	3	2
J	2	2
Anapl.	4	4
Unclassified	6	7
Localisations		
Bone marrow	34	40
Spleen	29	31
Liver	18	17
GI tract	16	17
Lung	16	13
Bone	13	12
Head and neck	10	7
CNS	10	12
Skin	4	7
Ann Arbor stage		
$I+I_E$	7	5
$II+II_E$	15	14
III	8	10
IV	70	71
B symptoms	58	57
LDH>1.N	62	66
β_2 microglobulin >3 mg/l	48	51
Serum albumin <30 g/l	23	24
Tumour size ⩾10 cm	52	51
Extranodal sites ⩾2	35	34
ECOG performance status		
0,1	64	60
⩾2	36	40
International Index		
Low risk (0, 1)	14	13
Low-intermediate (2)	26	25
High-intermediate (3)	32	34
High risk (4, 5)	28	28

Response

Response to treatment was assessed in 785 of the 810 patients. For 25 patients, the precise evaluation of response was not available owing to the absence of adequate restaging. At the end of induction in arm A (Figure 1), 58.5% of the patients had CR or CRu. 17% had PR, 9% showed failure and 16% died. In arm B, 48% had CR or CRu. 21% had PR, 8% showed failure and 23% died ($P=0.049$).

Arm A (ACVB) had a better CR rate (58.5%) than arm B (48%) ($P=0.003$). At the end of treatment in arm A, 52% had CR or CRu, 8% PR, 21% failure and 18% died, in arm B, 48% had CR or CRu, 11% PR, 15% failure and 26% died. The CR rate was 52% for arm A and 48% for arm B ($P=0.19$). The initial difference disappeared at the end of the treatment because, in arm B, 15% of the CR progressed and 35% of the PR obtained a CR, as compared with 18 and 29%, respectively, in arm A. Logistic regression analysis of response identified three independent parameters: (1) stage III IV ($P=0.0003$, RR 2.62: 1.57–4.44); (2) ECOG ⩾2 ($P=0.0012$, RR 2.08: 1.34–3.26); and (3) B induction arm ($P=0.0256$, RR 1.43: 1.04–1.95) were associated with poor response (no CR or CRu).

Toxicity

Death during treatment occurred in 18% of cases in arm A and 26% of cases in arm B. Death was due to toxicity, whether or not associated with progression in 70% of cases, to progression of lymphoma only in 8% and to other causes in 22%. Fourteen per cent of the patients who died during treatment were in CR.

Severe neutropenia (>grade 2) occurred in the majority of patients during the first course (89% in arm A, 87% in arm B). The occurrence of severe thrombocytopenia (>grade 2) was comparable in both arms (28%). Severe infection (>grade 2) during induction was 42% in arm A and 49% in arm B. Death from infection during induction was 9% in arm A and 14% in arm B. These toxicities never increased in proportion to the age of the patients, but always in proportion to the IPI score (Table 2).

Table 2 Toxicity

	According to arm			*According to score*				
	Arm A (%)	*Arm B* (%)	*P*	*Low* (%)	*Low-int.* (%)	*High-int.* (%)	*High* (%)	*P*
Severe neutropenia (>grade 2) after first course	89	87	NS	81	84	90	93	0.001
Severe thrombocytopenia (>grade 2) after first course	28	28	NS	5	18	30	44	0.001
Severe infection (>grade 2) after first course	42	49	0.066	26	37	49	57	0.012
Death from infection during induction	9	14	0.066	4	11	11	15	0.012

Survival

Event-free survival calculated at five years was 30% (95% CI: 28–32) (for arm A: 33% (95% CI: 30–36) and for arm B: 28% (95% CI: 26–30)) ($P=0.0289$) (Figure 2). Overall survival at five years was 38% (95% CI: 36–40) (for arm A: 40% (95% CI: 38–42) and for arm B: 36% (95% CI: 34–38)) ($P=0.068$) (Figure 3). Depending on the IPI score (low, low-intermediate, high-intermediate and high risk), the percentages of five-year survival were respectively 52% (47–57), 48% (44–52), 33% (30–36), 26% (23–29) ($P<0.0001$) (Figure 4). No difference between the two arms was observed when data were stratified according to the IPI score.

In univariate analysis, male-sex; involvement of BM, spleen, liver or CNS; advanced stage; B symptoms; LDH or β_2 elevation; low albumin level; two or more extranodal sites; and poor performance status were associated with poor prognosis. The Cox model identified ECOG ≥ 2 ($P=0.001$); BM involvement ($P=0.0078$); albumin <30 g/l ($P=0.0176$) and LDH ($P=0.0405$) as independent adverse prognosis factors. Arm B (alternating regimen) was a marginally significant ($P=0.0624$) independent factor for predicting a poor prognosis.

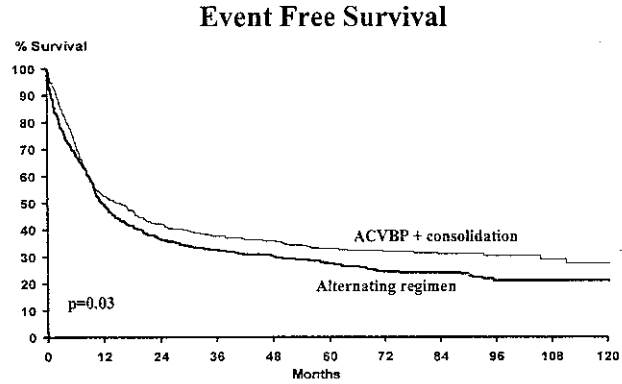

Figure 2 Event-free survival according to randomisation arms. ACVBP+consolidation is superior to alternating regimen ($P=0.03$).

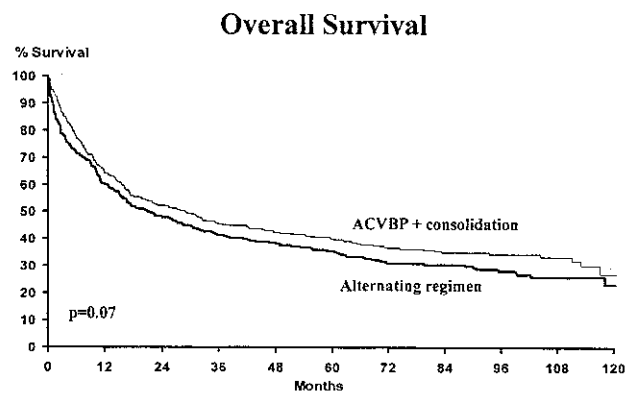

Figure 3 Overall survival according to randomisation arms. The difference is not statistically significant ($P=0.07$).

Discussion

The population included in this trial, ineligible for myeloablative chemotherapy in the absence of growth factors, was tested to receive a more intensive chemotherapy than the standard CHOP regimen. The selection of these poor-risk patients was made on the basis of prognostic factors determined prior to initiating treatment at start of study. In accordance with IPI classification, only 13% of this population was at low-risk (0 or 1 factor).

In this population of elderly, poor-risk patients, the toxicity of both arms was high, with 18 and 26% of deaths at the end of consolidation. Respectively, 9 and 14% of patients in Arm A and Arm B died from infection. Non-infectious toxic deaths were due to cardio-respiratory failures or to metabolic disturbances (tumour lysis syndrome). Deaths were related to severe infection and to progression or toxicity in 70% of cases. Most patients died at the time when response was not complete or not assessable. A high level of BM involvement and the high proportion of poor performance status may explain this high level of mortality.

In younger populations, ACVBP plus consolidation is the reference arm for treatment[2] and is associated with a small proportion (4%) of toxic deaths.

The basis of this study was to test the principle of the alternating regimen as previously described.[4,5] The first attempts to test this hypothesis were the MACOP-B regimen[6] or ProMACE-CytaBOM.[7] However, in a prospective randomised trial,[1] the simple CHOP regimen was shown to have the same efficacy as MACOP-B or ProMACE-CytaBOM.

In our study, for the alternation with ACVBP, we chose drugs active in relapsing patients: ie Ifosfamide,

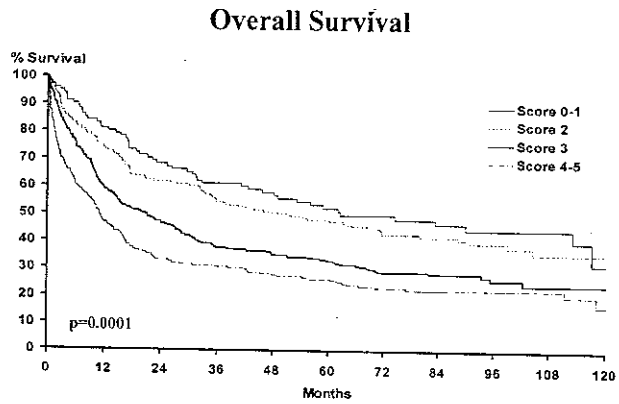

Figure 4 Overall survival according to IPI score. The difference is highly significant ($P=0.0001$).

VP16 or VM26, mitoxantrone, methyl-GAG and methotrexate (MIME or VIM[9–11] protocols). Other active drugs (platinum and high-dose AraC) were not used because of their known toxicity in elderly patients.[18]

Our results in a larger number of patients are comparable to those previously published Phase III studies testing alternating *vs* conventional regimens. The EORTC study[19] ($n=184$) compared a CHOP-like regimen (CHVmP-VB) with the alternating ProMACE-MOPP regimen ($n=162$) reported a higher C rate for CHVmP-VB (61%) than for ProMACE-MOPP (48%) ($P<0.0005$), but survival rates were not different. A German study[20] comparing CHOEP (CHOP+ etoposide $n=95$) with an alternating regimen (hCHOP/IVEP $n=90$) observed no difference in CR rate, survival or EFS. A UK study comparing B-CHOP-M (167 patients) with alternation of PEECM and B-CHOP-M (158 patients) showed no difference in CR rate, or relapse-free and overall survival.[21]

We observed, as in the EORTC study, a better CR rate for a non-alternating regimen, and no difference in terms of survival was observed in either arm. This absence of difference remains even after stratification of risk factors. Thus, no advantage can be demonstrated for an alternating regimen. Moreover, in our study, as in the EORTC study, the alternating regimen was more toxic.

Our results do show that ACVBP plus sequential consolidation was superior to the alternating regimen in terms of EFS. An improved EFS could be related to a higher CR rate at the end of induction. However, CR rate at the end of the treatment was not different and this was probably related to there being no difference in OS.

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Appendix

The GELA Group comprises the following centres in France: Lyon-Chalon-sur-Saone/Valence (B Coiffier, G Salles, P Biron, C Sebban, B Salles, Y Peaud) (160 patients); Paris St-Louis (C Gisselbrecht, P Brice, P Marolleau) (55 patients); Strasbourg (R Herbrecht, F Maloisel) (44 patients), Créteil (F Reyes, C Haioun, M Divine) (43 patients); Lille/Lens/Valenciennes (B Dupriez, M Simon, JP Jouet) (41 patients); Toulouse (M Attal, C Nouvel) (40 patients); Besançon (E Deconinck, A Rozenbaum) (35 patients); Rouen (H Tilly, A Stanatoullas) (34 patients); Limoges/StPriez en Jarez (D Bordessoule, J Jaubert) (31 patients); Chambery/Annecy (M Blanc, C Martin) (25 patients); Marseille/Avignon (R Bouabdallah, O Boulat) (23 patients); Nancy (P Lederlin, A Guerci) (23 patients); Paris Hôtel-Dieu/Foch/Suresnes (E Baumelou, L Chauvenet) (19 patients); Paris Pitié-Salpêtrière (J Gabarre) (18 patients); Reims (B Pignon) (17 patients); Mulhouse/Colmar (Eisenmann, B Audhuy) (14 patients); Bordeaux (J Reiffers) (nine patients); Pontoise (Y Kerneis) (nine patients); Bligny/Corbeil/Juvisy Evry (C Ferme) (eight patients); Clamart (G Tertian) (eight patients); Dijon (D Caillot) (eight patients); Rennes Laval (R Leblay, Jacomy) (eight patients); Paris Lariboisière/Val de Grâce (G Tobelem, G Auzanneau) (seven patients); Metz/Thionville (B Christian, Platini) (seven patients); Antibes/Nice (Dor A Thyss) (seven patients); Caen (O Reman) (six patients); Beaujon Clichy (M Dumont) (six patients); Clermont-Ferrand (P Travade) (four patients); Mont-pellier/Nimes (JF Rossi) (four patients); Le Mans (P Solal-Celigny) (three patients); Praz-Coutant (S Drony) (two patients); Réunion (C Garnier) (two patients); Blois (P Laplaige) (one patient); Compiègne (D Zylberait) (one patient); and in Belgium: UCL Yvoir (A Bosly, C Doyen) (24 patients), UCL Bruxelles (A Ferrant, N Straetmans) (29 patients), ULG Sart-Tilman Liège (G Fillet, Y Beguin) (20 patients), Jolimont La Louvière (A Delannoy) (eight patients), Gilly (P. Mineur) (10 patients).