

A PROSPECTIVE, RANDOMIZED TRIAL OF AUTOLOGOUS BONE MARROW TRANSPLANTATION AND CHEMOTHERAPY IN MULTIPLE MYELOMA

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ABSTRACT

Background The median survival of patients with myeloma after conventional chemotherapy is three years or less. Promising results have been reported with high-dose therapy supported by autologous bone marrow transplantation. We conducted a randomized study comparing conventional chemotherapy and high-dose therapy.

Methods Two hundred previously untreated patients under the age of 65 years who had myeloma were randomly assigned at the time of diagnosis to receive either conventional chemotherapy or high-dose therapy and autologous bone marrow transplantation.

Results The response rate among the patients who received high-dose therapy was 81 percent (including complete responses in 22 percent and very good partial responses in 16 percent), whereas it was 57 percent (complete responses in 5 percent and very good partial responses in 9 percent) in the group treated with conventional chemotherapy ($P < 0.001$). The probability of event-free survival for five years was 28 percent in the high-dose group and 10 percent in the conventional-dose group ($P = 0.01$); the overall estimated rate of survival for five years was 52 percent in the high-dose group and 12 percent in the conventional-dose group ($P = 0.03$). Treatment-related mortality was similar in the two groups.

Conclusions High-dose therapy combined with transplantation improves the response rate, event-free survival, and overall survival in patients with myeloma. (N Engl J Med 1996;335:91-7.)

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FOR the past 30 years, a combination of melphalan and prednisone has been the standard treatment for myeloma. Extensive trials of other drug combinations have not led to major improvements in clinical outcome. Myeloma remains an incurable malignant tumor with a median survival that does not exceed three years.^{1,2}

High-dose therapy has been evaluated in patients with myeloma. McElwain et al. reported that high doses of melphalan could induce a high rate of response even in patients with disease refractory to conventional doses of the drug.^{3,4} However, myelosuppression was prolonged. Barlogie et al. found that

the myelotoxicity of high-dose melphalan was reduced in patients who underwent autologous bone marrow transplantation.^{5,6} One consequence of that report is the use of transplantation to treat an increasing number of patients with myeloma.⁷

Although high-dose therapy with transplantation is promising in patients with myeloma,³⁻²⁵ selection bias hinders a direct comparison of the reported results with those of conventional chemotherapy. Prospective, randomized trials are needed to compare conventional chemotherapy with high-dose therapy combined with transplantation. In 1990, the Intergroupe Français du Myélome began a trial designed to address this issue.

METHODS

Criteria for Enrollment

Patients less than 65 years of age who had Durie-Salmon stage II or III myeloma²⁶ were eligible for the study. The criteria for exclusion were prior treatment for myeloma, another type of cancer, abnormal cardiac function (systolic ejection fraction < 50 percent or an abnormal stress test), chronic respiratory disease (vital capacity or carbon monoxide diffusion, < 50 percent of normal), abnormal liver function (serum bilirubin, > 2.0 mg per deciliter [$> 35 \mu\text{mol per liter}$]; or serum aminotransferase values more than four times the normal value), and psychiatric disease. Between October 1990 and May 1993, 204 patients from 32 French centers and 1 Belgian center were enrolled. Four patients were excluded, two each because of age over 65 years and violations of the study protocol (the use of allogeneic transplantation to improve a first response). Two hundred patients in all were evaluated. The study was approved by the institutional ethics committees, and the patients gave informed consent.

Study Protocol

Randomization

The patients were randomly assigned to one of the two treatment groups at the time of diagnosis. The sequence of random-

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*Additional centers and investigators participating in the study are listed in the Appendix.

ization was determined by the coordinating center (at Toulouse), which issued each treatment assignment by telephone after the patient's eligibility for the study was confirmed.

Conventional-Dose Chemotherapy

The protocol consisted of alternating cycles of combinations of chemotherapeutic agents, known as VMCP and BVAP. The VMCP regimen included vincristine (1 mg intravenously on day 1), melphalan (5 mg per square meter of body-surface area orally on days 1 to 4), cyclophosphamide (110 mg per square meter orally on days 1 to 4), and prednisone (60 mg per square meter orally on days 1 to 4). The BVAP regimen included vincristine (1 mg intravenously on day 1), carmustine (30 mg per square meter intravenously on day 1), doxorubicin (30 mg per square meter intravenously on day 1), and prednisone (60 mg per square meter orally on days 1 to 4). These alternating cycles of VMCP and BVAP were administered at 3-week intervals for 12 months, for a total of 18 cycles. Recombinant interferon alfa was administered three times a week in a dose of 3 million U per square meter from cycle 9 until the occurrence of any relapse.

High-Dose Therapy

After four to six alternating cycles of VMCP and BVAP (according to the availability of facilities at the bone marrow-transplantation center), patients with a performance status below grade 3 according to the criteria of the World Health Organization, a serum creatinine level under 1.7 mg per deciliter (150 μ mol per liter), and bone marrow (collected after cycle 4) that contained more than 200 million nucleated cells per kilogram of body weight underwent unpurged transplantation after preparation with melphalan (140 mg per square meter) and total-body irradiation (8 Gy delivered in four fractions over a four-day period, without lung shielding). Treatment with interferon alfa was started after hematologic reconstitution following the transplantation (granulocyte count, >1500 per cubic millimeter; platelet count, >75,000 per cubic millimeter).

Criteria for a Response

A complete remission was defined as the absence of a paraprotein on electrophoresis of serum and urine and 5 percent or fewer plasma cells with normal morphologic features in a bone marrow aspirate (the absence of paraprotein was not confirmed in all cases by immunofixation). A return of normal immunoglobulins was not included in the definition. A very good partial response was defined as a decrease of 90 percent in the serum paraprotein level; a partial response as a decrease of 50 percent in the serum paraprotein level (in patients who had Bence Jones protein) and a decrease of 90 percent in Bence Jones protein; a minimal response as a decrease of 25 percent in the serum paraprotein level; stable disease as no change in the paraprotein level; progressive disease as an increase of 25 percent in the serum paraprotein level after two cycles of the initial chemotherapy; and a relapse as the reappearance of the paraprotein, the recurrence of bone marrow infiltration (which was evaluated every six months) in a patient with a complete response, or both, and a 50 percent increase in paraprotein above the "plateau" level in two samples obtained four weeks apart in a patient with a response. The response of bone lesions was not studied in this trial, and no centralized review of bone lesions was performed.

Statistical Analysis

The proportions of patients with a given characteristic were compared by the chi-square test or by Fisher's exact test. Differences in the means of continuous measurements were tested by Student's t-test and checked by the Mann-Whitney U test. All tests were two-tailed. The duration of event-free survival was calculated for all patients from the date of randomization until the time of progression of disease, relapse, death, or the date the patient was last known to be in remission. Curves for event-free sur-

vival and overall survival were plotted according to the method of Kaplan and Meier and were compared by the log-rank test. Prognostic factors for overall survival and event-free survival were determined by the Cox proportional-hazards model in the analysis of covariates. The following variables were included in the univariate analysis: age, Durie-Salmon stage, the isotype of the monoclonal (M) component, beta₂-microglobulin level, bone marrow plasmacytosis, and treatment group. The objective was to compare the two treatment groups with respect to survival. The random assignment of at least 100 patients to each treatment group was needed to ensure a 5 percent level of significance and a power of 80 percent if the true probabilities of survival five years after diagnosis were 10 percent in the conventional-dose group and 50 percent in the high-dose (and transplantation) group. The study was completed after 200 patients were enrolled. All randomized patients were studied in their assigned treatment groups on an intention-to-treat basis.

RESULTS

Base-Line Characteristics

Table 1 shows the base-line characteristics of the 200 patients. No significant differences were found between the treatment groups.

Completion of Assigned Therapy

The patients enrolled in the conventional-dose group received a median of 18 cycles (range, 2 to 18) of VMCP and BVAP. Seventy-four patients enrolled in the high-dose group underwent transplantation. The median time from diagnosis to transplantation was 5.5 months (range, 4 to 11). Among the 26 patients who did not undergo transplantation, 5 died prematurely, 6 had poor performance status, 5 had abnormal renal function, and 10 had insufficient amounts of bone marrow in the sample collected. These exclusions were related to the age of the patients, since 12 of 67 patients 60 years of age or less (18 percent) did not undergo transplantation, as compared with 14 of 33 patients over 60 years of age (42 percent, $P=0.01$).

One hundred forty-three patients received interferon alfa (73 in the conventional-dose group and 70 in the high-dose group). Interferon alfa was introduced sooner after diagnosis in the conventional-dose group than in the high-dose group (mean [\pm SD] number of months before treatment, 8 ± 2.8 vs. 10 ± 3.2 ; $P=0.01$). Eighty-six patients (43 in each group) had to discontinue this treatment (9 because of thrombocytopenia and 77 because of relapse). Interferon alfa was administered for a median of 12 months in the conventional-dose group and 11 months in the high-dose group.

Response Rate

Before transplantation (i.e., after four cycles of chemotherapy), the response rate was similar in the two treatment groups. As compared with conventional chemotherapy, high-dose therapy with transplantation improved the response rate ($P<0.001$) (Table 2); 38 percent of the patients in the high-

TABLE 1. CHARACTERISTICS OF THE PATIENTS ACCORDING TO THEIR ASSIGNED DOSES OF CHEMOTHERAPY.*

CHARACTERISTIC†	CONVENTIONAL DOSE (N = 100)	HIGH DOSE (N = 100)	ALL PATIENTS (N = 200)
Sex (M/F)	45/55	57/43	102/98
Age (yr)	58±5.2	57±6.4	57.4±6
Duric-Salmon stage (no. of patients)			
II	23	28	51
III	77	72	149
M component (no. of patients)			
IgG	55	56	111
IgA	25	31	56
Bence Jones protein	17	11	28
IgD	3	2	5
Hemoglobin (g/dl)	11±2	11±2	11±2
Serum calcium (μmol/liter)	2.5±0.4	2.4±0.4	2.5±0.4
Serum albumin (g/liter)	39±9	39±7	39±8
Lactate dehydrogenase (IU)	230±131	264±155	250±145
Serum creatinine (μmol/liter)	115±81	112±80	113±80
Bone marrow plasmacytosis (% of cells)	36±25	39±25	38±25
Serum beta ₂ -microglobulin (mg/liter)	5±4.4	4.5±4	4.8±4

*Plus-minus values are means ±SD. None of the characteristics differed significantly between the two groups.

†To convert values for calcium to milligrams per deciliter, divide by 250. To convert values for creatinine to milligrams per deciliter, divide by 88.4.

dose group had complete or very good partial responses, as compared with 14 percent of the patients in the conventional-dose group. Furthermore, 43 percent of the patients in the conventional-dose group did not have partial responses, as compared with 19 percent of those in the high-dose group. Factors significantly associated with complete or very good partial responses were M component, the level of beta₂-microglobulin in serum, and the treatment-group assignment (Table 3).

Event-free and Overall Survival

In the conventional-dose group, treated with chemotherapy only, the median follow-up of the surviving patients was 37 months (range, 26 to 60; standard deviation, 8) from the time of randomization. The median event-free survival was 18 months, and the median overall survival 37.4 months. The probabilities of event-free survival and overall survival for five years after the diagnosis were 10 percent and 12 percent, respectively (Fig. 1 and 2). Fifty-two patients died, 47 because of the progression of disease and 5 because of the toxic effects of treatment.

In the high-dose group, treated with four cycles of chemotherapy and transplantation, the median follow-up of the surviving patients was 41 months (range, 22 to 60; standard deviation, 11) from the time of randomization. The median event-free sur-

vival was 27 months, and the median survival has not been reached as of this writing. The probabilities of event-free survival and overall survival for five years after the diagnosis were 28 percent and 52 percent, respectively (Fig. 1 and 2). The high-dose group had significantly longer event-free (P=0.01) and overall (P=0.03) survival than the conventional-dose group (Fig. 1 and 2). Thirty-seven patients in the high-dose group died, 30 because of the progression of disease and 7 because of the toxic effects of treatment (including 2 transplantation-related deaths).

Prognostic Factors for Event-free and Overall Survival

In the multivariate analysis of all 200 patients, event-free survival was significantly related to the level of beta₂-microglobulin in serum (P<0.001) and the treatment assignment (P=0.01). Overall survival was related only to the level of beta₂-microglobulin (P<0.001).

To appreciate better the effect of transplantation on survival, we analyzed the group of 122 patients who were 60 years of age or younger. Among these patients, most of those assigned to the high-dose group (82 percent) actually underwent transplantation. In a multivariate analysis of these younger patients, survival was related to the treatment assignment (P=0.03) and the level of beta₂-microglobulin (P<0.001). The probability of survival for five years after diagnosis was 18 percent in the conventional-dose group and 70 percent in the high-dose group (P=0.02) (Fig. 3).

To assess the response to treatment as one of the variables tested for their effect on survival, we analyzed the subgroup of 178 patients who survived more than one year after diagnosis. In this multivariate analysis, the presence of a response to treatment was related to survival (P<0.001). The five-year probability of survival after diagnosis was 72 percent

TABLE 2. RESPONSE RATES ACCORDING TO TREATMENT GROUP.*

TYPE OF RESPONSE	CONVENTIONAL DOSE (N = 100)	HIGH DOSE (N = 100)
	no. of patients	
Complete	5	22
Very good partial	9	16
Partial	43	43
Minimal	18	7
Progressive disease	25	12

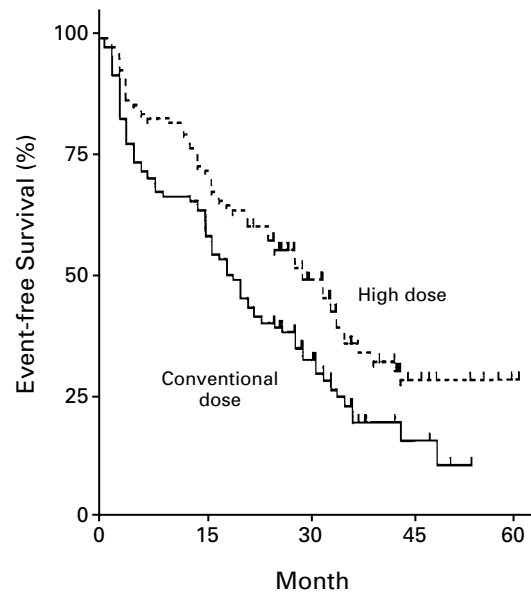
*P<0.001 for the comparison of the various response categories between the two groups by the chi-square test. Seventy-four patients in the high-dose group underwent autologous bone marrow transplantation.

(95 percent confidence interval, 42 to 91 percent) among 51 patients who had complete or very good partial responses, 39 percent (95 percent confidence interval, 23 to 58 percent) among 81 patients who had partial responses, and 0 among 46 patients who did not have even partial responses.

The High-Dose Group

Seventy-four patients in the high-dose group underwent transplantation. The median proportion of plasma cells in the bone marrow graft was 9 percent (range, 0 to 50 percent; standard deviation, 14). The median duration of neutropenia (<500 cells per cubic millimeter) and thrombocytopenia after transplantation was 18 days (range, 7 to 49; standard deviation, 7.7) and 22 days (range, 7 to 60; standard deviation, 10), respectively. There were two transplantation-related deaths (from staphylococcus and streptococcus septicemia in one patient each; 27 percent).

Of the 74 patients who underwent transplantation, 22 (30 percent) had complete responses, 16 (22 percent) had very good partial responses, and 32 (43 percent) had partial responses. A low level of beta₂-microglobulin in the serum was the only significant predictor of a complete or a very good par-



Conventional dose 58 (48–68) 32 (23–42) 15 (7–28) 10 (3–27)
High dose 71 (61–79) 50 (39–55) 28 (18–40) 28 (18–40)

Figure 1. Event-free Survival According to Treatment Group. The numbers shown below the time points are probabilities of event-free survival (the percentages of patients surviving event-free) and 95 percent confidence intervals.

TABLE 3. BASE-LINE CHARACTERISTICS OF THE PATIENTS WITH COMPLETE OR VERY GOOD PARTIAL RESPONSES.

VARIABLE	COMPLETE OR VERY GOOD PARTIAL RESPONSE	P VALUE
	no. of patients/ no. studied (%)	
All patients	52/200 (26)	—
Sex		0.70
Male	25/102 (24)	
Female	27/98 (28)	
Age (yr)		0.60
≤60	34/122 (28)	
>60	18/78 (23)	
Duric-Salmon stage*		0.08
II	18/51 (35)	
III	34/149 (23)	
Isotype of monoclonal gammopathy		0.02
IgG	19/111 (17)	
Others (IgA)	33/89 (37)	
Plasma cells in marrow (%)		0.50
≤30	24/84 (29)	
>30	28/116 (24)	
Beta ₂ -microglobulin (mg/liter)		0.05
≤4	36/110 (33)	
>4	15/79 (19)	
Treatment group		<0.001
Conventional dose	14/100 (14)	
High dose	38/100 (38)	

*The stage was determined according to the classification system of Duric and Salmon.²⁶

tial response (P=0.01). The probabilities of event-free survival and overall survival five years after the diagnosis were 39 percent and 68 percent, respectively. There was no significant relation between the percentage of plasma cells in the graft and event-free survival.

Salvage Therapy

In the conventional-dose group, 50 patients relapsed. Five patients received no salvage therapy, 36 received either the VAD regimen (a continuous intravenous infusion of 0.4 mg of vincristine per square meter and 9 mg of doxorubicin per square meter over a 24-hour period for four days, with 40 mg of oral dexamethasone per day on days 1 through 4) or another regimen of conventional chemotherapy, and 9 received high-dose therapy (140 mg of melphalan per square meter, with or without total-body irradiation) supported by autologous hematopoietic stem cells. With a median follow-up among the surviving patients of 11 months from the time of relapse, the probability of survival for two years after relapse was 25 percent in the conventional-dose group (95 percent confidence interval, 12 to 44 percent).

In the high-dose group, 46 patients relapsed. Five patients received no salvage therapy, 33 received the VAD regimen or another form of conventional chemotherapy, and 8 received high-dose melphalan (140

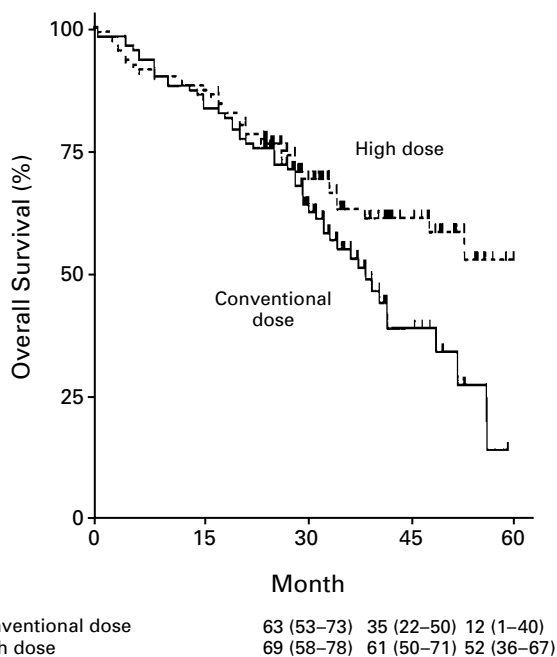


Figure 2. Overall Survival According to Treatment Group. The numbers shown below the time points are probabilities of overall survival (the percentages of patients surviving) and 95 percent confidence intervals.

mg per square meter) supported by autologous hematopoietic stem cells. With a median follow-up among the surviving patients of 15 months from the time of relapse, the probability of survival for two years after relapse was 35 percent in the high-dose group (95 percent confidence interval, 18 to 57 percent), a proportion not significantly different from that in the conventional-dose group.

DISCUSSION

Alkylating agents and prednisone have been the standard therapy for myeloma for the past three decades.^{1,2,27,28} The rates of response to this treatment range from 40 to 60 percent, but the median duration of survival does not exceed three years. The combination of alkylating agents with vincristine and doxorubicin has not had better results than therapy with melphalan and prednisone.²⁹ The value of maintenance treatment with interferon alfa in prolonging the response and survival³⁰ has been assessed in randomized trials, which found that the effect of interferon alfa on survival, if any, is marginal.³¹⁻³⁶ In our trial, there was a response rate of 57 percent and a median survival of three years in the conventional-therapy group despite the combined use of VMCP, BVAP, and interferon alfa.

High-dose therapy has been reported to improve survival in myeloma when given to patients with newly diagnosed disease.³⁻²⁵ These results are difficult to

assess because the recruitment of patients for transplantation is subject to a selection bias with regard to age, performance status, and renal function. Our trial, which was designed to avoid these sources of bias, demonstrates that high-dose therapy improves both event-free and overall survival. The probability of event-free survival for five years after the diagnosis was 12 percent in the conventional-dose group and 28 percent in the group treated with high-dose therapy and transplantation ($P=0.01$). Survival in these two groups was 12 percent and 52 percent, respectively ($P=0.03$). A study by the Southwest Oncology Group³⁷ comparing high-dose therapy with conventional chemotherapy confirms our results. The data in that study justify the further development of high-dose therapy programs. The optimal timing of these treatments remains to be determined. In our trial, transplantation was performed as part of the initial therapy. Whether delayed transplantation, given at the time of a progression of disease, would have similar results will be clarified in ongoing trials.^{37,38}

An objective of our trial was to evaluate the feasibility and toxic effects of transplantation. Twenty-six percent of patients assigned to this treatment could not receive it. The most common reasons were poor

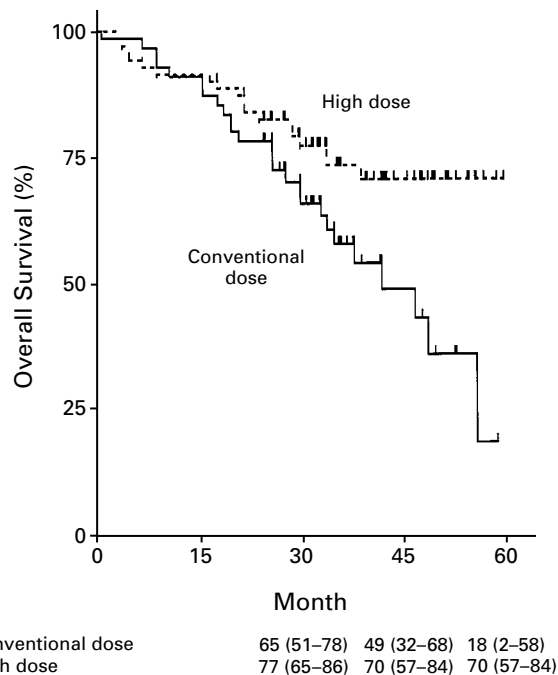


Figure 3. Overall Survival According to Treatment Group in Patients 60 Years Old or Less. The numbers shown below the time points are probabilities of overall survival (the percentages of patients surviving) and 95 percent confidence intervals.

performance status and insufficient bone marrow collection, due to the poor response rate observed after the initial regimen of VMCP and BVAP. Initial chemotherapy with a regimen such as VAD, which can induce responses in 70 to 80 percent of patients after two to three cycles,³⁹ could lower the exclusion rate. The risk of life-threatening toxic effects in the high-dose group was a major concern, but transplant-related deaths occurred in only 2 of the 74 patients. The rate of death from toxic effects was similar in both groups. Hematopoietic growth factors, reported to improve the recovery of neutrophils after transplantation, were not administered in our trial.^{40,41} The duration of severe marrow aplasia may be shorter in patients given peripheral-blood stem cells than in those supported with autologous marrow.^{20,42} We are evaluating this possibility.

In our trial the probability of event-free survival for five years after the diagnosis was only 28 percent among the patients in the high-dose group. Strategies to improve these results are warranted. Our results demonstrate that a complete response is the most important prognostic factor for survival. It is plausible that a high rate of complete response may be attained with more aggressive therapy. The absence of a plateau in the curve for event-free survival among our patients justifies the development of new strategies to control any residual disease after transplantation. Interleukin-2, interleukin-4, retinoids, B-cell-directed immunotoxins, and vaccination with idiotypes are being investigated.

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APPENDIX

The following additional centers and investigators from the Intergroupe Français du Myélome participated in this study:

Alençon, Centre Hospitalier Général (N. Frenkiel); Angers, Centre Hospitalier Régional et Universitaire (C. Foussard); Annecy, Centre Hospitalier d'Annecy (B. Corront); Avignon, Hôpital Henri Duffaut (A.M. Touchais, G. Lapeu); Brest, Hôpital Augustin Morvan (C. Autrand); Cahors, Centre Hospitalier Régional (S. Lassoued); Cannes, Clinique du Méridien (S. Dides, H. Naman); Carcassonne, Centre Hospitalier Général (G. Morlock); Castres, Centre Hospitalier Général (P. Pitié); Colmar, Centre Hospitalier Louis Pasteur (F. Kohser); Grenoble, Hôpital Albert Michallon (B. Pegourié, L. Molina); Lyon, Centre Léon Bérard (P. Biron); Lyon, Hôpital Edouard Herriot (M. Michallet); Lorient, Centre Hospitalier Bodélio (C. Rives); Marseilles, Institut Paoli Calmettes (R. Bouabdallah); Montauban, Clinique du Pont de Chaume (A. Redon); Montpellier, Centre Val D'Aurèle (M. Fabbro); Nancy, Centre Hospitalier Brabois (A.P. Guerici); Nice, Hôpital du Cimiez (N. Gratecos, B. Taillan); Nice, Centre Antoine Lacassagne (A. Thyss); Niort, Centre Hospitalier Général (D. Arlhac); Perpignan, Centre Hospitalier Général (J. Camo); Poitiers, Centre Hospitalier La Milleterie (A. Sadoun, M.C. Desmarest); Reims, Hôpital Robert Debré (B. Pignon);

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