Improved Management of Invasive Pulmonary Aspergillosis in Neutropenic Patients Using Early Thoracic Computed Tomographic Scan and Surgery

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Purpose: **The prognosis of invasive pulmonary aspergillosis (IPA) occurring in neutropenic patients remains poor. We studied whether new strategies for early diagnosis could improve outcome in these patients.**

Patients and Methods: **Twenty-three histologically proven and 14 highly probable IPAs in 37 hematologic patients (neutropenic in 36) were analyzed retrospectively.**

Results: **The most frequent clinical signs associated with IPA were cough (92%), chest pain (76%), and hemoptysis (54%). Bronchoalveolar lavage (BAL) was positive in 22 of 32 cases. *Aspergillus* antigen test was positive in 83% of cases when tested on BAL fluid. Since October 1991, early thoracic computed tomographic (CT) scans were systematically performed in febrile neutropenic patients with pulmonary x-ray infiltrates. This approach allowed us to recognize suggestive CT halo signs in 92% of patients, compared with 13% before this date, and the mean time to IPA diagnosis was reduced dramatically from 7 to 1.9 days. Among 36 assessable patients, 10 failed to respond (amphotericin B [AmB] plus fluorocytosyne, n = 2; itraconazole + AmB, n = 8) and died of aspergillosis. Twenty-six patients were cured or improved by antifungal treatment (itraconazole with or without AmB, n = 22; voriconazole, n = 4). In 15 of 16 cases, surgical resection was combined successfully with medical treatment. Achievement of hematologic response, early diagnosis, unilateral pulmonary involvement, and highest level of fibrinogen value < 9 g/L were associated with better outcome.**

Conclusion: **In febrile neutropenic patients, systematic CT scan allows earlier diagnosis of IPA. Early antifungal treatment, combined with surgical resection if necessary, improves IPA prognosis dramatically in these patients.**

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FOR THE PAST 30 years, increasing doses of chemotherapeutic agents have been used to improve the response rate in hematologic malignancies. This strategy was associated with an increased incidence of systemic fungal infections.[1,2] Invasive pulmonary aspergillosis (IPA) is the second most common cause of fungal infection in immunocompromised patients. Its prognosis remains poor in leukemic patients, despite amphotericin B (AmB) treatment. The mortality rate reaches 50% to 60% when IPA occurs during chemotherapy-induced neutropenia and could exceed 90% in the setting of bone marrow transplantation (BMT).[3] Improvement of prognosis needs early recognition of IPA and effective antifungal treatment.[4,5]

The present study analyses the course of IPA in 37 patients with hematologic malignancy and suggests that systematic use of thoracic computed tomography (CT) could allow earlier diagnosis in the course of IPA and thereby improve overall survival among these patients.

PATIENTS AND METHODS

Patients and Conditions of Hospitalization

Between January 1988 and February 1996, 501 patients with hematologic malignancies received 754 myeloablative treatments that induced neutropenia (polymorphonuclear leukocyte [PMN] count < 500/μL). Among these intensive therapies, 219 BMTs were performed. During the neutropenia that followed chemotherapy, patients were hospitalized in single-isolation reverse rooms or in laminar air-flow -protected rooms. In these rooms, chest x-rays were taken systematically twice a week. Microbiologic monitoring included a daily blood culture and samples from the throat, nose, urine, and stool twice a week. Axillary temperature was measured every 3 hours. When the first febrile episode (axillary temperature > 38°C for > 3 hours) occurred, β-lactam antibiotic plus aminoglycoside was used as empirical therapy after microbiologic sampling and a chest x-ray. Antibiotic therapy was adapted secondarily to the results of cultures. When these cultures were negative and fever persisted, vancomycin or teicoplanin was added at 48 hours. Amphotericin B (AmB) was administered when either the fever persisted for 24 to 48 hours following the addition of a glycopeptide, or a subsequent episode of fever occurred in a patient with ongoing neutropenia.

CT Scan Criteria for IPA Suspicion in Neutropenic Patients

The identification of a chest x-ray infiltrate during a febrile episode in a neutropenic or BMT patient resulted in a systematic search for

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invasive aspergillosis. In neutropenic patients, thoracic CT scan is a major tool for the diagnosis of IPA. Two CT signs are clearly identified as indicators of IPA. The CT halo sign is described as a mass-like infiltrate with a surrounding halo of ground-glass attenuation. This halo sign is highly indicative of IPA and occurs early in the course of IPA during the neutropenic period.[8,8] The air-crescent sign is described as a pulmonary cavitation. It is a later sign that appears with bone marrow recovery.[9,10] This air-crescent sign is not pathognomonic of aspergillosis, but in the setting of patients with hematologic malignancies, and especially in leukemic patients, it is highly suggestive of filamentous fungal disease.[10,11] Therefore, a thoracic CT scan was performed as frequently as possible to search for CT signs of IPA. A high-resolution CT scan was used in all cases, with 10-mm-thick sections and additional 1-mm-thin sections through any suspected fungal lesions

Other Criteria for IPA Suspicion

Minor signs of IPA (rated as chest pain; hemoptysis, including hemoptysic sputum; and proof of *Aspergillus* in the nasal secretions or in the expectorations) were recorded systematically. To clarify the diagnosis, a fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) was performed depending on the patient's condition. Direct examination and culture of BAL were realized systematically. At the time of suspected IPA, an *Aspergillus* antigen test was performed on repeated serum samples (Pastorex test; Pasteur Institute, Paris, France). In some cases, an *Aspergillus* antigen test was performed on the BAL fluid.

When possible, a transbronchial biopsy was performed during fiberoptic examination. In some patients, a pulmonary resection of suspected aspergillary mass was realized either under thoracoscopy or in an open thoracotomy. In other cases, biopsy of an affected extrapulmonary organ was performed. In all of these cases with tissue biopsy, pathologic and mycologic examinations were performed.

Criteria for IPA Diagnosis

Definite IPA was defined as positive tissue biopsy with typical septate acute branching hyphae with or without positive culture for *Aspergillus*. In the absence of histopathology, the combination of a positive BAL test for *Aspergillus* (direct examination and/or culture) and a suggestive thoracic CT scan (halo or air-crescent signs) was considered as a highly probable IPA.

Treatment of IPA

Until August 1988, the treatment of IPA relied on AmB, either alone or in combination with fluorocytosine. Since that time, most patients have been treated with oral itraconazole (Janssen-Cilag Lab, Boulogne, France) alone or in combination with AmB. In some cases, plasmatic levels of itraconazole were measured with high-performance liquid chromatography (HPLC) or microbiologic assays. More recently, a few patients received a new azole compound, namely, voriconazole (Pfizer Lab, Kent, United Kingdom), which is available in both oral and intravenous forms.

Statistical Analysis

The characteristics of patients with definite IPA and highly probable IPA were compared by the Mann-Whitney U test and Fisher's exact test.

Survival curves were plotted according to the Kaplan-Meier method and survival duration were compared by the log-rank test. Survival of patients with IPA relied on outcome of both hematologic disease and fungal disease. Since the death of patients attributed to IPA always occurred in the 3 months following IPA diagnosis, we have chosen to censor the analysis of survival 100 days after IPA diagnosis to analyze the aspergillosis-related factors that influence patient outcome.

RESULTS

Patients

Between January 1988 and February 1996, we managed 754 episodes of bone marrow aplasia in patients with hematologic diseases. Pneumonia was identified in 159 cases, either during neutropenia or in the weeks following aplasia recovery. In 37 patients, pneumonia was identified as IPA (5%). The main characteristics of these patients are listed in Table 1.

Hematologic malignancies included acute leukemia (n = 32), chronic myeloid leukemia (n = 1), lymphoma (n = 1), myeloma (n = 2), and severe aplastic anemia (n = 1). Two patients had recently received allogenic BMT and three patients were in hematologic relapse after autologous BMT. At the time of IPA diagnosis, 20 patients (54%) had progressive hematologic disease (failure or relapse) and all but one (allogenic BMT) were neutropenic for a median length of 20 days (range, 8 to 43).

Aspergillosis occurred during six of 303 myeloablative treatments (2%) performed in laminar air-flow–protected rooms, compared with 31 of 451 treatments (7%) performed in single reverse-isolation rooms, which suggests the efficacy of laminar air-flow protection in preventing aspergillosis ($P = .005$, χ^2 test).

Diagnosis of Aspergillosis

The criteria for IPA diagnosis are listed in Table 1. We compared the characteristics of patients with definite IPA (n = 23) and those with highly probable IPA (n = 14). None of the clinical, biologic, or radiologic signs were significantly different between the two groups.

Clinical signs associated with IPA included cough, fever more than 39°C, and chest pain in most patients, while hemoptysis occurred in half (hemoptysic sputum in most patients, except four patients who either died of massive hemoptysis in two cases or needed a pulmonary resection or an arterial embolization in one case each, respectively).

Fibrinogen level was systematically measured each other day during hospitalization. It was found to be greater than 6 g/L in most patients (median value, 7 g/L; range, 5.5 to 11.4) in the 48 hours before IPA diagnosis.

Since the diagnosis of IPA was established or highly suspected, *Aspergillus* antigenemia was measured in all but three patients. In eight patients, antigenemia was mea-

Table 1. Criteria for Diagnosis in 37 Cases of IPA

Variable	All Patients With IPA (N = 37)		Patients With Definite IPA (n = 23)		Patients With Highly Probable IPA (n = 14)	
	No	%	No	%	No	%
Main characteristics of patients						
Mean age (years)	50.6 ± 15		48.3 ± 15		53.8 ± 16	
Sex ratio (male/female)	1.18		1.30		1.00	
Acute leukemia	32/37	86	21/33	91	11/14	79
Progressive hematologic disease	20/37	54	13/23	56	7/14	50
Previous neutropenia (days)	20.1 ± 7.4		21.1 ± 7.7		18.3 ± 7.1	
Clinical signs associated with IPA						
Fever > 39°C before IPA diagnosis	32/37	86	19/23	83	13/14	93
Mean duration of fever (days)	6.1 ± 5.3		7.3 ± 6		5.2 ± 4	
Cough	34/37	92	20/23	87	14/14	100
Chest pain	28/37	76	18/23	78	10/14	71
Hemoptysis (including minor hemoptysis)	20/37	54	13/23	56	7/14	50
Indirect biologic signs associated with IPA						
Fibrinogen level ≥ 6 g/L (at time of IPA diagnosis)	32/37	86	20/23	87	12/14	86
Positive *Aspergillus* antigenemia the day of IPA diagnosis	4/34	12	2/20	10	2/14	14
Positive *Aspergillus* antigenemia after IPA diagnosis	10/34	29	8/20	40	2/14	14
Positive *Aspergillus* antigen test in the BAL fluid	15/18	83	8/10	80	7/8	88
Positive sputum sample for *Aspergillus*	11/37	30	7/23	30	4/14	29
Positive nasal sample for *Aspergillus*	1/37	3	1/23	4	0/14	0
Direct biologic signs associated with IPA						
Patients with BAL performed	32/37	86	18/23	78	14/14	100
Positive culture of BAL for *Aspergillus*	22/32	69	8/18	45	14/14	100
Positive tissue biopsy	23/37	62	23/23	100	Not done	
Radiologic signs associated with IPA						
No. of pulmonary focus x-rays ≥ 2	29/37	78	17/23	74	12/14	86
Biloteral focus on x-ray	23/37	62	14/23	61	9/14	64
Patients with thoracic CT	33/37	89	19/23	83	14/14	100
Thoracic CT halo sign	27/33	82	16/19	84	11/14	79
Thoracic CT air-crescent sign	6/33	18	3/19	16	3/14	21

sured from one to three times per patient after IPA diagnosis and was positive in only one. In the 26 remaining patients, antigenemia was measured from five to 35 times per patient (median, 10) and was positive in 13. From IPA diagnosis, antigenemia was found positive after a median delay of 4.5 days (range, 0 to 23). Overall, among 34 patients in whom antigenemia was performed, four (12%) were positive on the day of IPA diagnosis, 10 (29%) were positive after IPA diagnosis, and 20 (59%) remained negative for antigenemia. Overall, only 72 of the 291 antigen tests performed were positive (25%), including two patients with 16 and 25 positive consecutive tests.

BAL was performed in 32 patients. In 22 cases (69%), *Aspergillus* was found by direct examination and/or in the culture. *Aspergillus* antigen test was identified as positive in BAL fluid from 15 of 18 examined cases (83%). In 10 cases, culture and antigen were both positive in BAL. Conversely, antigen was positive in five of eight cases with negative culture of BAL. Interestingly, IPA diagnosis was established definitely by pathologic examination in these five patients. The cultures of sputum and nose samples were positive for *Aspergillus* in 11 (30%) and one (4%) patient, respectively.

In all cases, chest x-ray showed at least one pulmonary infiltrate. This lesion was unique in only eight of 37 studied cases (22%). Pulmonary involvement was multiple and bilateral in most (Table 1). Thoracic CT scan was always highly suggestive of IPA. It identified a CT halo sign in 16 of 19 patients with definite IPA and a CT air-crescent sign in the remaining three. In the other group, CT halo and air-crescent signs were recorded in 11 and three of 14 patients, respectively. In all but two patients (with one CT), at least two thoracic CT scans were performed. The first CT scan always suggested aspergillosis.

A tissue biopsy (including three transbronchial biopsies) or resection was performed in 23 patients (lungs, 15 cases; lungs and bone, one; lungs and larynx, one; lungs and thyroid, one; bronchi, two; maxillary sinuses and skin, one case; larynx, one; pericardium, one). In all cases, histopathologic analysis showed invasion of the tissue by branching septate hyphae. The culture of the tissue biopsy

showed the presence of *Aspergillus* in 19 of 21 cases in which it was performed. In 16 cases, pulmonary resection of the aspergillary mass was performed. Preoperative criteria of IPA diagnosis and operative procedures are listed in Table 2. In four cases (25%), preoperative diagnosis of IPA was highly suspected on the combination of suggestive CT and evidence of *Aspergillus* in BAL. Interestingly, in the 12 remaining cases (75%), the main criteria of IPA diagnosis before surgery was based on CT findings, either alone or in combination with a positive antigen test on BAL fluid (five cases).

Thirty-three strains of *Aspergillus* were isolated. *Aspergillus fumigatus* and *Aspergillus flavus* grew in 29 and three cases respectively. *Aspergillus nidulans* was isolated in one case. AmB was active in vitro on 31 of 33 strains tested. Itraconazole was tested on 19 isolated strains of *Aspergillus* (Centre National de Reference des Mycoses et des Antifongiques, Professor Bertrand Dupont; Institut Pasteur, Paris, France). Itraconazole had good in vitro activity against the 19 strains tested (median minimal inhibitory concentration [MIC], 0.36 μg/mL; range, 0.01 to 2.5).

The time between the first clinical warning sign and IPA diagnosis was determined retrospectively, based on the date of fever, cough, or chest pain occurrence. On average, the time to diagnosis was 3.6 ± 4 days for all patients. Until October 1991, chest CT scans were used only to document IPA in patients whose diagnosis had already been confirmed or strongly suspected. Since then, CT has been used systematically for the early diagnosis of aspergillosis (Table 3). Thoracic CT performed before October 1991 was the first evidence of IPA (with the presence of halo sign) in only one of eight patients, compared with 23 of 25 after this date ($P = .0001$, Fisher's exact test). Because of this approach, an earlier diagnosis of IPA could be attained. The time between the first clinical sign and IPA diagnosis was shorter after October 1991 than before (1.9 ± 1.5 days *v* 7 ± 5.5 days; $P = .01$, Mann-Whitney U test). This reduction of the time to reach IPA diagnosis was associated with a better prognosis. Before October 1991, the deaths of six of 12 patients were directly attributed to IPA. Since this date, only four of 24 assessable patients died of IPA ($P = .04$, Fisher's exact test) (Fig 1).

At the time of the first clinical sign of IPA, 21 patients (57%) were receiving intravenous AmB (administered empirically before the IPA diagnosis for fever of unknown origin) for a median of 13 days (range, 6 to 43) at a mean daily dose of 1 ± 0.27 mg/kg/d.

Antifungal Therapy and Clinical Outcome

Currently, 36 patients are assessable for antifungal response.

Ten patients died of IPA (28%). All of them received AmB (median dose, 1.5 mg/k/d) for a median duration of 12 days (range, 8 to 30) combined with either fluorocytosine (median dose, 150 mg/kg/d) in two or itraconazole (median dose, 400 mg/d) in the eight remaining patients until death. The plasmatic levels of itraconazole were determined in six patients and the residual levels of itraconazole remained low (< 0.2 μg/mL) during the 20 first days of treatment in five of them. Eight patients in

Table 2. Pulmonary Surgical Resection in 16 Cases of IPA

Variable	Preoperative IPA Diagnosis Based on Evidence of *Aspergillus* on BAL and on Suggestive Thoracic CT	Preoperative IPA Diagnosis Based on Suggestive Thoracic CT Without Evidence of *Aspergillus* on BAL
No of patients	4 (25%)	12 (75%)
Chest pain before surgery	3/4	9/12
Hemoptysis before surgery	3/4	5/12
Positive *Aspergillus* antigenemia before surgery	0/4	1/12
Positive culture of sputum before surgery	3/4	1/12
Performed BAL before surgery	4/4	7/12
Positive BAL for *Aspergillus* before surgery	4/4	0/7
Positive *Aspergillus* antigen test in BAL before surgery	3/3	5/7
Thoracic CT halo sign before surgery	3/4	11/12
Thoracic CT air-crescent sign before surgery	1/4	1/12
Pulmonary resection under thoracoscopy	1/4	2/12
Pulmonary resection under open thoracotomy	3/4	10/12
Pulmonary segmentectomy or wedge resection	1/4	4/12
Pulmonary lobectomy	3/4	8/12
Surgery to prevent hemoptysis (emergency procedure)	2/4	6/12
Histologically confirmed diagnosis of IPA	4/4	12/12
Positive culture to tissue biopsy	4/4	8/10

Table 3. Contribution of Systematic CT Scan for Early Diagnosis of IPA

Variable	Before October 1991	After October 1991	P
IPA observed	12	25	NA
Patients with positive tissue biopsy	8/12	15/25	NS*
Patients with positive culture of BAL	9/12	13/19	NS*
Mean time (days)			
Admission to hospital to IPA diagnosis	31 ± 9	21 ± 5	.0006†
First IPA sign to IPA diagnosis	7 ± 5.5	1.9 ± 1.5	.01†
Patients with chest CT scans	8/12 (66%)	25/25 (100%)	.008*
CT scan with suggestive halo sign before IPA diagnosis	1/8	23/25	0001*
Death (for assessable patients) attributed to IPA	6/12 (50%)	4/24 (17%)	.04*

Abbreviation: NA, not applicable.
*Fisher's exact test.
†Mann-Whitney *U* Test.

hematologic failure remained neutropenic following IPA diagnosis and died of extensive pulmonary aspergillosis. Two patients, who had achieved complete hematologic responses, died of massive hemoptysis. The median survival duration was 20 days (range, 9 to 90).

Twenty-six patients (72%) were improved or cured by antifungal treatment. Twenty-two patients received itraconazole (median dose, 400 mg/d) for a median length of 302 days (range, 103 to 1,185). No severe adverse reactions were experienced with itraconazole therapy. The plasmatic levels of itraconazole were determined in 16 patients, and in 14 of them the residual levels of itraconazole were greater than 0.6 μg/mL during the 20 first days of treatment. In 13 cases, AmB (median dose, 1.3 mg/kg/d) was combined with itraconazole for a median duration of 9 days (range, 5 to 20). Three patients were successfully treated with voriconazole (median dose, 6 mg/kg/d; median duration, 63 days). One patient failed to respond to a 26-day treatment with voriconazole and improvement of IPA was achieved with itraconazole. Overall, apyrexia was achieved on average within 9 days (range, 2 to 22), while the fibrinogen level normalized (< 4 g/L) within 40 days (range, 10 to 100). In 19 of 26 cases (73%), a complete hematologic response was achieved. The median length of neutropenia after initiation of antifungal therapy was 5 days (range, 1 to 80). In five of 26 cases, patients were considered improved by the treatment. These patients died of underlying disease within 6 months following IPA diagnosis without any evidence of aspergillosis. The 21 remaining patients were considered cured of aspergillosis. Eleven patients are still well and alive, while 10 patients died of underlying hematologic disease more than 6 months following IPA diagnosis without any sign of aspergillosis. Overall, the median survival duration after IPA diagnosis was 390 days (range, 112 to 2,039) in this group.

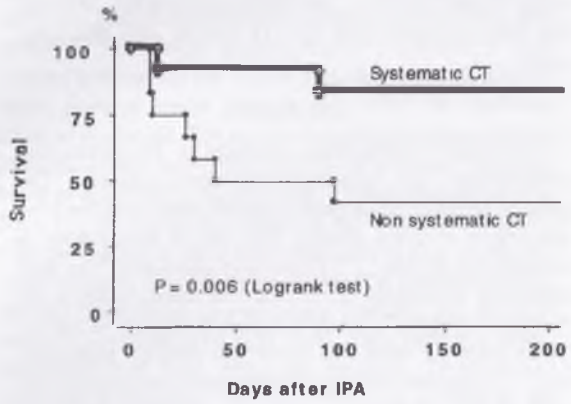

Fig 1. Kaplan-Meier survival curves according to the strategy for IPA diagnosis. Systematic thoracic CT scan in febrile neutropenic patients since the end of 1991 was associated with improved survival of patients with an IPA diagnosis.

Pulmonary Surgery Combined With Antifungal Treatment

Among 16 patients who underwent pulmonary surgical resection, the surgery was performed as either a diagnosis (four cases) or a therapeutic procedure (12 cases) combined with medical therapy (Table 2).

In four cases, surgery was delayed after IPA diagnosis for more than 3 weeks (median, 34 days; range, 21 to 548). Pulmonary resection (wedge resection in two cases and lobectomy in two) of a peripheral residual mass was performed due to continuing hemoptysis in one case and stable aspergillary lesion despite medical therapy before new courses of myeloablative therapy in three other (including two allogenic BMTs). The four patients had recovered from bone marrow aplasia with a normal count of platelets and granulocytes at the time of surgery.

In the remaining eight cases, surgery was an emergency procedure. The need for surgical interventions was based

on observation of repeated chest CT scans that showed pulmonary aspergillosis that contacted the pulmonary artery or its dividing branches with a risk of massive hemorrhage due to angioinvasive fungal process. Interestingly, in six of eight patients, the IPA diagnosis before surgery was based on CT findings alone (combined with positivity of a positive *Aspergillus* antigen test on the BAL in one case). Lobectomy was performed in all of the cases. Six patients underwent surgery despite persistent granulocytopenia. Before surgical intervention, the platelet counts were less than 100,000/μL in seven cases. These seven patients received two to six U packed platelets to reach a count greater than 100,000/μL. No postoperative bleeding was observed. Macroscopic analysis of the lobectomy sections showed necrotic aspergillary focus at the point of contact with the pulmonary artery, accompanied in six cases by an invasion of the arterial wall and bearing an increased risk of hemorrhage (in one case, the main left pulmonary artery ruptured during surgical intervention). Pathologic examination and culture of the surgical sections confirmed invasive aspergillosis in all of the cases. Surgery was uneventful, and seven patients were discharged from hospital less than 3 weeks after surgery, while one patient died of extensive aspergillary pneumonia 12 days after surgery.

Prognostic Factors for Survival

The lack of a complete hematologic response to chemotherapy and the related increase of neutropenia duration are negative predictors for prognosis. Eight of 10 patients who did not respond to antifungal therapy versus seven of 26 responding patients were in hematologic failure (P = .005, Fisher's exact test). Overall, 13 of 26 patients improved or cured by antifungal treatment received further myeloablative treatments (including two allogenic and one autologous BMT) in the year following IPA diagnosis without any relapse of IPA.

The 24 assessable patients treated for IPA since October 1991 had an improved survival (Fig 1) compared with the 12 patients treated before this date (P = .006, log-rank test).

The 12 patients with a highest fibrinogen level ≥ 9 g/L in the 10 days after IPA diagnosis had a unfavorable outcome (Fig 2) compared with the 24 patients with a highest value fibrinogen level that was less than 9 g/L (P = .0002, log-rank test).

Additionally, the 14 patients with initial unilateral pulmonary focus had a better outcome (Fig 3) compared with the 22 patients with a bilateral pulmonary focus (P = .02, log-rank test).

The value of these three prognostic factors was

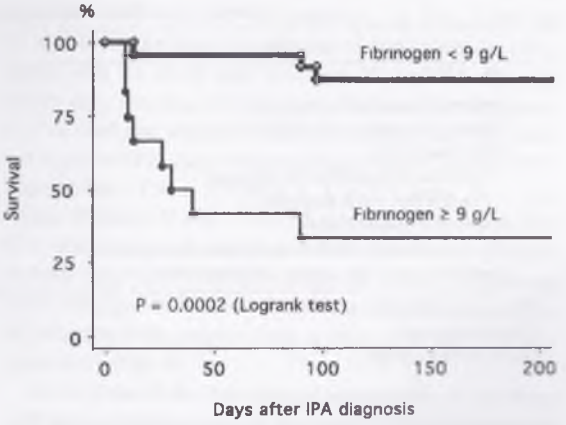

Fig 2. Kaplan-Meier survival curves according to the highest level of fibrinogen in the 10 days after IPA diagnosis. A fibrinogen value > 9 g/L was associated with a poor outcome.

strengthened by the multivariate analysis. In the Cox model, poor prognosis was related to fibrinogen level ≥ 9 g/L during the 10 days after IPA diagnosis [P = .003; relative risk (RR): 8.7; 95% confidence interval (CI): 2.1 to 36.9] and to delayed treatment before systematic use of CT scan (P = .02; RR: 3.6; 95% CI: 1.0 to 13.5). Lastly, a trend for unilateral pulmonary involvement as a favorable prognostic factor was identified (P = .058; RR: 0.08; 95% CI: 0.01 to 0.66).

The prognostic influences of BMT and residual plasma levels of itraconazole were not determined due to the small cohort of patients in these groups. Only two patients have received an allogeneic T-cell-depleted BMT. One patient died from disseminated aspergillosis during an acute GVHd episode 2 months after alloBMT, whereas the other survived more than 18 months after IPA diagnosis.

DISCUSSION

Pulmonary aspergillosis remains a life-threatening complication for immunocompromised patients.[3] The present series of neutropenic patients does not differ from previously reported studies. The risk of aspergillosis is estimated to be 5%.[1,12,13] Eighty-five percent of IPAs were observed in patients hospitalized in rooms without air-filtration systems,[14] and the length and severity of neutropenia were the main risk factors for invasive aspergillosis.[15] The median duration of neutropenia before diagnosis was 20 days. Only one patient with allogenic BMT was not neutropenic at the time IPA occurred.

The characteristics of patients with definite or highly probable IPA did not differ significantly (Table 1). Acute

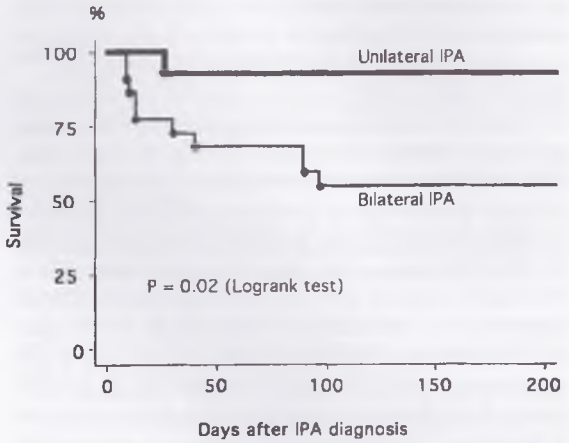

Fig 3. Kaplan-Meier survival curves according to initial pulmonary involvement by aspergillosis. Bilateral involvement was associated with a poor outcome.

leukemia was the most common underlying hematologic disease.[1] The other main clinical indicators of aspergillosis were chest pain and hemoptysis, which were observed with a frequency of 76% and 54%, respectively.[16,17] Fever is a common problem in neutropenic patients. All of the patients who developed IPA had fever greater than 38°C. Interestingly, 86% of patients demonstrated fever greater than 39°C in the days before IPA diagnosis.

The positivity of *Aspergillus* antigenemia is highly predictive of invasive aspergillosis in immunocompromised patients, although its sensitivity remains weak.[18-20] In our experience, the antigen test was positive in 14 of 34 patients tested and was a relatively good indicator of fungal infection. Repeating the assays seems to increase the sensitivity.[18,19] However, antigenemia was positive in only 12% of patients on the day of IPA diagnosis. In 29% of cases, positive results were obtained after the establishment of diagnosis. The use of a sandwich enzyme-linked immunosorbent assay (ELISA) could increase the sensibility of *Aspergillus* antigenemia.[20] When identified in the BAL (15 of 18 positive results in our study), *Aspergillus* antigen appears to be a good indicator of IPA in neutropenic patients.[23] In five patients with IPA diagnosis subsequently established by pathologic examination, the antigen test was positive on BAL fluid, while culture or direct examination of BAL remained negative. Therefore, in a febrile neutropenic patient with x-ray infiltrates, the positivity of *Aspergillus* antigen in the BAL fluid could have the same value as the isolation of *Aspergillus* in the BAL.

Of 32 BALs performed, 69% showed *Aspergillus*, a rate comparable to other reports.[21,22] In the group of 23 patients with a definitely proven diagnosis of IPA, a BAL was performed in 18 cases and was positive for *Aspergillus* in only eight. However, the presentation of patients with definite IPA and those with highly probable IPA was similar. The isolation of *Aspergillus* in expectoration or nasal swab must be considered when diagnosing aspergillosis in leukemic patients.[24] In this report, *Aspergillus* was isolated in expectoration from 30% of patients and isolation of *Aspergillus* in nasal swab was not helpful in the diagnosis of IPA.

The contribution of chest CT scan to the diagnosis of pulmonary aspergillosis may be helpful. Previous studies reported that the halo sign was highly indicative of IPA in neutropenic patients.[5-8,25] The image occurs early in the disease and allows the assumption of aspergillosis before the typical cavitation.[6,7,9,25,26] Therefore, we assigned major diagnostic importance to CT scans and, in particular, to the halo sign. At the beginning, we used CT scans for confirmation of aspergillosis that had already been diagnosed through other means and frequently observed cavitations. Since the end of 1991, chest CT scan has been part of the routine examination for the etiologic diagnosis of radiographic infiltrates that occur in febrile neutropenic patients. Accordingly, CT scans performed since that time have most often contributed to the diagnosis, with the presence of at least one halo sign in greater than 90% of cases (Table 3). Moreover, in 12 of 16 patients who underwent pulmonary resection, the criteria for the diagnosis of aspergillosis were mainly the existence of febrile pneumopathy in neutropenic patients and the presence of either a halo sign (n = 11) or air-crescent sign (n = 1) in thoracic CT scans (Table 2). These observations indicate that early chest CT scans tend to provide earlier diagnosis of aspergillosis in neutropenic patients. Interestingly, since the end of 1991, the prognosis of neutropenic patients with IPA has been improved due to earlier diagnosis (Fig 1 and Table 3).

Traditional treatment of aspergillosis in immunocompromised patients is AmB.[3] In leukemic patients, especially in allogenic BMT patients, the efficacy of AmB was limited, with a failure rate that ranged from 50% to 90%.[3] In the present series, both 13 of 26 patients improved by the treatment and the 10 patients who died of IPA received curative doses of AmB in the 10 first days of treatment. The use of a new AmB formulation (liposomal and lipidic emulsions) will need to be studied for the treatment of IPA in neutropenic patients.[27]

One way to improve the prognosis of IPA patients is earlier initiation of antifungal treatment.[5,28] This can be achieved through an earlier diagnosis, with the use of CT

scan.[25] In addition, the recent introduction of a new triazole antifungal agent, itraconazole, appears to improve the treatment of aspergillosis. Response rates in greater than 60% to 70% have been reported for invasive aspergillosis treated with itraconazole.[4,28,30,31] We had a similar experience for both our preliminary studies[32] and the present study, in which the overall response rate for patients treated with itraconazole was approximately 75%. In this report, patients who responded to itraconazole were treated for a minimum of 6 months if the immunodeficiency persisted or if the patient experienced a new course of myeloablative chemotherapy. The use of voriconazole seems to be interesting,[33] but the small number of cases does not allow conclusions.

The two main purposes of surgical treatment of IPA were the prevention of severe, sometimes fatal, hemoptysis,[17,34,35] and the reduction of a remaining *Aspergillus* mass before a new myeloablative treatment.[36] Most often, surgery was performed after the neutropenia had resolved. In our experiment, the death of two patients from massive hemoptysis led to prophylactic surgical resection of the aspergillary lesion when this lesion threatened the integrity of the pulmonary artery. Despite persistent granulocytopenia in six of eight patients, complications of the surgical procedure were minimal. In most of cases, observation of the excised mass showed necrosis with perforation of the pulmonary artery wall, which confirmed the need for intervention. In this urgent situation, the role of thoracic CT was major. When surgical intervention was practiced, the preoperative diagnosis of IPA was based on CT findings alone in six of eight cases. To determine the optimal time for surgical intervention, close consultation between the medical, surgical, and radiologic teams was required. Repeated chest CT scans with examination of the lesion were crucial factors to determine the need for surgery. The present series highlighted several prognostic factors. The major factor was the outcome of the hematologic malignancy. The achievement of a complete response with recovery of granulocyte counts was associated with a better outcome, even in the few months after IPA diagnosis. An early diagnosis of IPA in neutropenic patients is needed to improve the prognosis of the disease.[5,27] Since the end of 1991, we have modified our strategy of IPA diagnosis in febrile neutropenic patients with systematic use of thoracic CT to identify early CT halo signs. This reduction of the time to diagnosis IPA has resulted in better management of the disease with early initiation of antifungal therapy and increased overall survival (Fig 1). The fibrinogen value was also a prognostic factor. Neutropenic patients with IPA had a high level of fibrinogen in the days preceding and following the IPA diagnosis. Furthermore, a fibrinogen value greater than 9 g/L was associated with a negative outcome (Fig 2). Specific receptors for fibrinogen were identified on the surface of *A fumigatus*.[37] These receptors could act as mediators of conidial adherence to host tissue.[37] However, it is impossible to know whether the fibrinogen increase is the cause or the consequence of the progression of fungal disease. The value of fibrinogen could represent the importance of the aspergillary mass. The last parameter that influenced clinical outcome was bilateral versus unilateral pulmonary involvement (Fig 3).

In conclusion, although pulmonary aspergillosis in the neutropenic patient remains a life-threatening complication of myeloablative therapy, earlier diagnosis could greatly improve its prognosis. The use of chest CT scan for early detection allows earlier initiation of antifungal therapy. Itraconazole seems to be an efficacious treatment of IPA in immunocompromised patients. Thoracic surgery combined with medical therapy could prevent efficiently massive hemorrhage or be used as an adjuvant treatment. Nevertheless, the main prognosis factor for improvement remains the achievement of a complete hematologic response.

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REFERENCES

1. Bodey G, Bueltmann B, Duguid W, et al: Fungal infections in cancer patients: An international autopsy survey. Eur J Clin Microbiol Infect Dis 11:99-109, 1992

2. Pirsch JD, Maki DG: Infectious complications in adults with bone marrow transplantation and T-cell depletion of donor marrow. Increased susceptibility to fungal infection. Ann Intern Med 104:619-631, 1986

3. Denning DW, Stevens DA: Antifungal and surgical treatment of invasive aspergillosis: Review of 2121 published cases. Rev Infect Dis 12:1147-1201, 1990

4. Denning DW, Tucker RM, Hanson LH, et al: Treatment of invasive aspergillosis with itraconazole. Am J Med 86:791-800, 1989

5. Fisher BD, Armstrong D, Yu B, Gold JWM: Invasive aspergillosis. Progress in early diagnosis and treatment. Am J Med 71:571-577, 1981

6. Kuhlman JE, Fishman EK, Siegelman SS: Invasive pulmonary aspergillosis in acute leukemia: Characteristic findings on CT, the CT halo sign, and the role of CT in early diagnosis. Radiology 157:611-614, 1985

7. Potente G: Computed tomography in invasive pulmonary aspergillosis. Acta Radiol 30:587-90, 1989

8. Blum U, Windfuhr M, Buitrago-Tellez C, et al: Invasive pulmonary aspergillosis—MRI, CT, and plain radiographic findings and their contribution for early diagnosis. Chest 106:1156-1161, 1994

9. Gefter WB, Albelda SM, Talbot GH, et al: Invasive pulmonary aspergillosis and acute leukemia. Limitations in the diagnostic utility of the air crescent sign. Radiology 157:605-610, 1985

10. Mori M, Galvin JR, Barloon TJ, et al: Fungal pulmonary infections after bone marrow transplantation: Evaluation with radiography and CT. Radiology 157:605-610, 1991

11. Funada H, Misawa T, Nakao S, et al: The air crescent sign of invasive pulmonary mucormycosis in acute leukemia. Cancer 53:2721-2723, 1984

12. Cordonnier C, Bernaudin JF, Bierling P, et al: Pulmonary complications occurring after allogenic bone marrow transplantation. A study of 130 consecutive transplanted patients. Cancer 178:721-6, 1985

13. Pannuti CS, Gingrich RG, Pfaller MA, et al: Nosocomial pneumonia in adult patients undergoing bone marrow transplantation: A 9-year study. J Clin Oncol 9:77-84, 1991

14. Sherertz RJ, Belani A, Kramer BS, et al: Impact of air filtration on nosocomial *Aspergillus* infections. Am J Med 83:709-718, 1987

15. Gerson SL, Talbot GH, Hurwitz S, et al: Prolonged granulocytopenia: The major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. Ann Intern Med 100:345-351, 1984

16. Gerson SL, Talbot GH, Hurwitz S, et al: Discriminant scorecard for diagnosis of invasive pulmonary aspergillosis in patients with acute leukemia. Am J Med 79:57-64, 1985

17. Albelda SM, Talbot GH, Gerson SL, et al: Pulmonary cavitation and massive hemoptysis in invasive pulmonary aspergillosis. Influence of bone marrow recovery in patients with acute leukemia. Am Rev Respir Dis 131:115-120, 1985

18. Manso E, Montillo M, De Sio G, et al: Value of antigen and antibody detection in the serological diagnosis of invasive aspergillosis in patients with hematological malignancies. Eur J Clin Infect Dis 13:756-760, 1994

19. Andriole VT: Infections with *Aspergillus* species. Clin Infect Dis 17:481-486, 1993 (suppl 2)

20. Verweij PE, Stynen D, Rijs AJMM, et al: Sandwich enzyme-linked immunosorbent assay compared with Pastorex latex agglutination test for diagnosing invasive aspergillosis in immunocompromised patients. J Clin Microbiol 33:1912-1914, 1995

21. Albelda SM, Talbot GH, Gerson SL, et al: Role of fiberoptic bronchoscopy in the diagnosis of invasive pulmonary aspergillosis in patients with acute leukemia. Am J Med 76:1027-1034, 1984

22. Kahn FW, Jones JM, England DM: The role of bronchoalveolar lavage in the diagnosis of invasive pulmonary aspergillosis. Am J Clin Pathol 86:518-523, 1986

23. Andrews CP, Weiner MH: *Aspergillus* antigen detection in bronchoalveolar lavage fluid from patients with invasive aspergillosis and aspergillomas. Am J Med 73:372-380, 1982

24. Yu YL, Muder RR, Poorsattar A: Significance of isolation of *Aspergillus* from the respiratory tract in diagnosis of invasive pulmonary aspergillosis. Result from a 3-year prospective study. Am J Med 81:249-254, 1986

25. Kuhlman JE, Fishman EK, Burch PA, et al: Invasive pulmonary aspergillosis in acute leukemia; The contribution of CT to early diagnosis and aggressive management. Chest 92:95-99, 1992

26. Hruban RH, Meziane MA, Zerhouni E, et al: Radiologic-pathologic correlation of the CT halo sign in invasive pulmonary aspergillosis. J Comput Assist Tomogr 11:534-536, 1987

27. Mills W, Chopra R, Linch DC, et al: Liposomal amphotericin B in the treatment of fungal infections in neutropenic patients—A single-centre experience of 133 episodes in 116 patients. Br J Haematol 86:754-760, 1994

28. Aisner J, Schimpff SC, Wiernick PH: Treatment of invasive aspergillosis: Relation of early diagnosis and treatment to response. Ann Intern Med 86:539-543, 1977

29. Dupont B: Itraconazole therapy in aspergillosis: Study in 49 patients. J Am Acad Dermato 23:607-614, 1990

30. De Beule K, De Doncker P, Cauwenbergh G, et al: The treatment of aspergillosis and aspergilloma with itraconazole, clinical results of an open international study (1982-1987). Mycoses 31:476-485, 1988

31. Denning DW, Lee JY, Hostetler JS, et al: NIAID Mycoses Study Group multicenter trial of oral itraconazole therapy for invasive aspergillosis. Am J Med 97:135-144, 1994

32. Caillot D, Casasnovas RO, Solary E, et al: Itraconazole as salvage therapy in invasive pulmonary aspergillosis occurring during amphotericin B therapy in neutropenic patients. Chemotherapy 38:50-51, 1992

33. Denning D, Del Favero A, Gluckman E, et al: UK-109,496, a novel, wide-spectrum triazole derivative for the treatment of fungal infections: Clinical efficacy in acute invasive aspergillosis. Proceedings of the American Society of Microbiology 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 17-20, 1995 (abstr F80)

34. Wong K, Waters CM, Walesby RK: Surgical management of invasive pulmonary aspergillosis in immuno-compromised patients. Eur J Cardiothorac Surg 6:138-143, 1992

35. Pagano L, Ricci P, Nosari A, et al: Fatal haemoptysis in pulmonary filamentous mycosis: An underevaluated cause of death in patients with acute leukaemia in hematological complete remission. A retrospective study and review of literature. Br J Haematol 89:500-505, 1995

36. Moreau P, Zahar JR, Milpied N, et al: Localized invasive pulmonary aspergillosis in patients with neutropenia—Effectiveness of surgical resection. Cancer 72:3223-3226, 1993

37. Annaix V, Bouchara JP, Larcher G, et al: Specific binding of human fibrinogen fragment D to *Aspergillus fumigatus* conidia. Infect Immun 60:1747-1755, 1992