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Invasive pulmonary aspergillosis in patients with hematologic malignancies: survival and prognostic factors

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Background and Objectives. Despite improvements made in its early diagnosis and effective treatment, invasive pulmonary aspergillosis (IPA) remains a devastating opportunistic infection. In this retrospective study we have reviewed all consecutive cases of IPA diagnosed in adult patients with hematologic malignancies in our center from 1995 to 2000 to determine survival and prognostic factors.

Design and Methods. Forty-one patients were included in the study. Ante-mortem classification of cases of IPA were: 4 definite, 10 highly probable, 19 probable and 8 possible cases; all these last eight patients were later upgraded to definite IPA at post-mortem examination. Clinical charts were reviewed and factors possibly affecting the outcome of IPA were analyzed.

Results. All but two patients received chemotherapy and/or immunosuppresive therapy before the onset of IPA (conventional chemotherapy = 24, allogeneic stem cell transplantation [SCT] = 12, autologous SCT = 3). At IPA diagnosis 28 patients were neutropenic ($< 0.5 \times 10^9$/L) for a median of 25 days (range 7-135), and 10 allogeneic SCT patients were receiving cortisteroids for graft-versus-host-disease. All but two patients received antifungal treatment for IPA. The median delay from diagnosis to start of therapy was two days (range 0-20). The median follow-up after the first symptom or sign of IPA was 42 days with a maximum follow-up of 61 months. The actuarial 4-month infection-free survival was 40% (95% CI 25% to 55%). Thirty-three patients died during follow-up and IPA was implicated in the patients' death in 24 cases (75%). In multivariate analysis prolonged survival was associated with recovery of neutropenia during treatment ($p = 0.001$) and not having received an allogeneic SCT ($p = 0.003$).

Interpretation and Conclusions. Despite prompt initiation of antifungal therapy, survival of patients with a hematologic malignancy and IPA is currently low. Perhaps the introduction of more sensitive diagnostic methods will allow the onset of intensive therapy prior to the appearance of more advanced clinical symptoms and/or radiological signs, and the time will come to test whether earlier and more intensive therapy will improve survival.

Key words: invasive pulmonary aspergillosis, prognostic factors, hematologic malignancy, radiological findings.

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The incidence of invasive aspergillosis (IA) has increased dramatically during the last decade. Recent data from 11,000 autopsy cases in Germany showed a progressive increase in the percentage of IA from 17% to 60%, over the years 1978-1992.[1] The most common site of IA is the lung.[2-5] Pannuti *et al.*[2] reported an overall incidence of invasive pulmonary aspergillosis (IPA) of 7.3% after hematopoietic stem cell transplantation (SCT), with an annual increase in the incidence from 3% to 10% during a 9-year study. IPA is a fulminant and highly fatal infection in patients with hematologic malignancies. The reported mortality rate is approximately 60% when IPA occurs during chemotherapy-induced neutropenia and could exceed 90% in the setting of SCT.[5]

Improvement of survival may rely on the early recognition of IPA and prompt initiation of antifungal treatment.[6-8] Early diagnosis of IPA is, however, a difficult obstacle. Definitive diagnosis is established by histologic examination of pulmonary tissue; however, invasive procedures are often contraindicated in the clinical setting of profound marrow aplasia or an impaired clinical condition due to acute pneumonia. Bronchoscopy with bronchoalveolar lavage (BAL) has a high specificity in this patient population, but a low sensitivity.[9] In histologically-proven IPA, the overall diagnostic sensitivity of BAL is 43%.[10] Typical computed tomography (CT) changes include the halo-sign during neutropenia or the air crescent sign or cavitary lesions in non-neutropenic hosts. These findings can be seen in up to 75% of patients with histologically-proven IPA.[11,12] However, IPA can also produce non-specific localized infiltrates and consolidation.[11,12] Detection of circulating galactomannan (GM) is a recent method used for the early diagnosis of IPA. Initial reports evaluating the serial screening for circulating GM by sandwich enzyme-linked immunosorbent assay show a sensitivity of 93% and a specificity of 95%.[13-15] Sulahian *et al.*[16] reported detection of GM antigenemia in most patients before the appearance of clinical

symptoms and before the onset of radiological signs of IPA.

However, despite these improvements in the early diagnosis of IPA, around 30% of cases remain undiagnosed and untreated at death.[17-19] We have reviewed all consecutive cases of IPA in adults with a hematologic malignancy seen in our institution during a period of six years, with the aim of analyzing possible prognostic factors for survival.

Design and Methods

Patients

We reviewed the medical records of all patients who developed IPA between January 1995 and December 2000. The adult Hematology Unit at Sant Pau Hospital consists of 19 high-efficiency particulate air-filtered rooms. During the study period, in our department prophylactic fluconazole was used only in recipients of an allogeneic SCT (alloSCT) who received corticosteroids, while prophylactic itraconazole was used in patients with a prior history of IA.

Forty-one consecutive adult patients with hematologic malignancies developed an IPA during the six-year study period. Patients who fulfilled the following criteria were included in the study: patients with a positive *post-mortem* diagnosis and/or with a proven, highly probable or probable diagnosis of IPA during life. Combining *ante-* and *post-mortem* findings, 18 patients were classified as having a definite IPA, 6 a highly probable IPA and 17 a probable IPA. Using only *ante-mortem* data, there were 4 definite, 10 highly probable, 19 probable and 8 unclassifiable cases; all these last eight patients were later upgraded to definite IPA at autopsy examination.

Definitions of IPA

Definite, highly probable and probable IPA were defined as follows:

Definite IPA: when a positive tissue biopsy was available.

Highly probable IPA: positive *Aspergillus spp.* cultures and/or fungal hyphae observed directly in BAL fluid or in two consecutive sputum samples accompanied by clinical and highly suggestive radiological (nodular peripheral lesion with a surrounding halo of ground glass attenuation or with air crescent sign or cavitation) evidence of IPA.

Probable IPA: negative cultures, but clinical and radiological evidence suggesting IPA.

Diagnostic methods

When a patient developed symptoms or signs of a pulmonary infection, a conventional chest X-ray was performed, usually followed by high-resolution chest CT. In patients with pulmonary infiltrates, fiberoptic bronchoscopy with BAL was carried out if the patient's clinical condition allowed it. Transbronchial biopsy was performed when patients had more than 50×10^9/L platelets. Standard microbiological methods for direct microscopy, culture and identification of fungi were used.[20] During the study period no antigen tests for *Aspergillus spp.* were used.

Data collection

Clinical, radiological and microbiological findings present at the time of and after the diagnosis of IPA were reviewed in detail, as were the treatment for and outcome of the fungal disease. Factors possibly affecting the outcome of IPA were recorded. Autopsy data were also reviewed when available.

Definitions of treatment responses

Response to antifungal treatment was defined according to previous criteria.[21]

Complete response: disappearance of all clinical symptoms and signs of IPA, as well as resolution of radiological findings.

Partial response: clinical and radiological improvement but not fulfilling the criteria for complete response.

Treatment failure: progression of the clinical and radiological lesions of IPA during therapy.

Statistical analysis

The main end-point was infection-free survival, which was calculated from the date of diagnosis to death from the infection. Patients who died from another cause with complete or partial response of the IPA were censored at the time of death and patients who were still alive were censored at the reference date of 31 December, 2000. The day of diagnosis was defined as the day of first symptom or sign of infection.

Clinical, radiological and microbiological characteristics of infection were summarized using descriptive statistics. Comparison of categorical variables between groups was performed by Fisher's exact test and comparison of continuous variables was performed by Mann-Whitney's U test.

Survival was estimated by using Kaplan-Meier method, and the prognostic significance of covariates was studied by the long rank test. All p values are two-sided and statistical significance was defined as a p value < 0.05. All covariates found to have a $p < 0.1$ were introduced into a Cox regression model for multivariate analysis. Relative hazard (with its 95% confidence interval) was estimated by a Cox regression model.

The following potential prognostic factors for infection-free survival were evaluated. Entered as categorical variables: gender, underlying disease, disease status, previous treatment for underlying disease, alloSCT, systemic steroid use and other immunosuppressive treatments, neutropenic status (neutrophil count < 0.5×10^9/L) at diagnosis, presence of hemoptysis, recovery of neutropenia after IPA diagnosis, radiological findings, extent of radiological lesions, use of CT for diagnosis, BAL results, use of empirical or prophylactic antifungal treatment, type of amphotericin B used for treatment, level of diagnostic category reached during life and recovery of a fungal pathogen during life. Entered as quantitative variables: age, duration of neutropenia after diagnosis, days between stem cell infusion or chemotherapy and diagnosis, and interval between diagnosis and treatment.

Since all deaths attributed to IPA occurred within 117 days from diagnosis, the figures that illustrate survival curves are censored at day 120 after diagnosis.

Results

Patients' characteristics

The patients' characteristics are shown in Table 1. The median age of the patients was 42 years (range, 19 to 67 years). Twenty-eight (68%) patients were neutropenic (< 0.5×10^9/L) at IPA diagnosis, 21 of them after conventional chemotherapy and five after high dose chemotherapy with SCT (autologous SCT, 3; alloSCT, 2). The other two patients were neutropenic due to refractory acute leukemia and severe aplastic anemia. The median duration of neutropenia was 25 days (range, 7 to 135 days). Fourteen (50%) out of 28 neutropenic patients had complete granulocyte recovery at a median of 6 days (range, 1 to 31 days) after the diagnosis of IPA. Ten out of 12 alloSCT patients had graft-versus-host-disease (GVHD: acute grade II-IV, 5; chronic extensive, 5) and all were receiving corticosteroids at the time of IPA for a median of 70 days (range, 9 to 378). In two patients the only risk factor for IA was having suffered prolonged neutropenia in the previous 30 days due to consolidation or salvage chemotherapy for acute leukemia. Prior to the onset of IPA, ten patients had received prophylactic fluconazole (100 - 200 mg/day iv or po) and two had received prophylactic itraconazole (400 mg/day).

Clinical presentation

Table 2 shows the prominent symptoms of IPA at diagnosis. Respiratory symptoms were present in 33 (80%) patients. In one of them these symptoms were associated with neurological symptoms and in another with symptoms of sinusitis. Two patients had skin lesions. Fever (axillary temperature > 38°C) within five days before the first symptom or sign of infection was present in 35 (85%) patients. Thirty-one patients were receiving broad spectrum-antibiotics and 18 empirical antifungal therapy (conventional amphotericin B [c-AmB] at a daily dose of 0.6 mg/kg or amphotericin B lipid complex [ABLC] at a dose of 1 mg/kg/day). For SCT patients the median time from stem cell infusion to the first symptom of IPA was 78 days (range, 0 to 447 days) and for non-SCT patients the median time from chemotherapy to the first symptom was 19 days (range, 0 to 54 days).

Table 1. Patients' characteristics at diagnosis of IPA.

	No. (%)
Male/female	26 / 15
Underlying disease	
AL, MDS	27 (66)
NHL, CLL, MM	7 (17)
CML	4 (10)
AA	3 (7)
Hematologic status	
AL diagnosis	13 (32)
CR1 or CP1	10 (24)
Advanced disease	18 (44)

AL: acute leukemia; AA: aplastic anemia; CHT: chemotherapy; CLL: chronic lymphocytic leukemia; CML: chronic myelogenous leukemia; CP1: first chronic phase; CR1: first complete remission; MDS: myelodysplastic syndrome; MM: multiple myeloma; NHL: non-Hodgkin's lymphoma.

Table 2. Presenting symptoms at IPA diagnosis.

Fever	35 (85%)
Respiratory symptoms	33 (80%)
Cough	18
Dysnea	15
Chest pain	10
Hemoptysis	5
Cutaneous aspergillosis	2
Neurological signs/symptoms	2
Sinusitis	1

Radiological findings

Pulmonary lung findings are detailed in Table 3. All but one patient had a chest-X ray performed at the time of the first respiratory symptom or sign. Additionally, a thoracic CT was performed in 30 (73%) patients within a median of 3 days (range, 0 to 20 days). Overall, X-ray studies showed bilater-

al pulmonary involvement in 26 (63%) patients. The CT *halo sign* was more frequent in neutropenic patients, most of whom were non-alloSCT recipients. On the other hand, nodular cavitated lesions were more frequent in non-neutropenic patients, most of whom were alloSCT recipients (Table 3). A brain scan was performed in two patients with neurological symptoms, showing brain abscesses in both cases. The patient with sinusitis had a CT scan showing involvement of the right frontal sinus with bone destruction.

Mycological data

Twenty-six BAL were performed in 22 patients. This procedure yielded positive results in 9 (35%) cases (culture alone, 5; microscopy alone, 1; both culture and microscopy, 3). Transbronchial biopsy was performed in two cases and showed invasive fungal hyphae with positive cultures in both. Two consecutive sputum samples were cultured for fungi in 18 patients and were positive in 4 (22%) cases. Based on *post-mortem* results (*see below*) the sensitivity of BAL was 57% and 22% for sputum cultures. We did not find differences in the radiological findings in patients with a positive or negative BAL: 5/16 with radiology suggesting IPA had positive BAL *versus* 4/6 with non-suggestive radiology; 5/13 with bilateral *versus* 4/9 with unilateral involvement, respectively. The median duration of prior treatment with AmB was 3.5 days for patients with a positive BAL versus 1.5 days for those with a negative BAL.

In 9 cases *Aspergillus spp.* were isolated from a lung sample, obtained either by lobectomy (n = 2) or at autopsy (n = 7). Combining BAL, sputum, lung and skin samples (n =2), 21 patients had a positive isolate for *Aspergillus spp.* The most frequent species isolated was *A. fumigatus* (n = 9), followed by *A. flavus* (n = 3), *A. niger* (n = 2), *A. terreus* (n = 2) and non-specified *Aspergillus spp.* (n = 5). In six cases the diagnosis of aspergillosis was based on a compatible histopathology with negative cultures.

Treatment of IPA

All but two patients received antifungal treatment. The median delay from diagnosis to start of therapy was 2 days (range, 0-20 days). In 20 patients (49%) antifungal treatment was started based on the results of a CT scan demonstrating suggestive lesions of IPA. In the other 11 patients treatment was started before the CT scan was performed. There were no differences in the median days from diagnosis to the start of treatment between patients in whom a CT scan was performed and those in whom it was not (2.5 days vs 1 day, $p = 0.4$) nor between patients with radiological signs suggesting IPA and those with non-suggestive radiology (2 days vs 4 days, $p = 0.9$).

Table 3. Radiological findings.

	Normal	*Diffuse infiltrates*	*Nodular lesions**	
	No. (%)	*No. (%)*	*Halo sign**	*Air-crescent sign or cavitation**
			No.(%)	*No.(%)*
Chest X-ray (n = 40)	13 (32.5)	24 (60)	0	3 (7.5)
Thoracic computed tomography (n = 30)	0	3 (10)	16 (53)	11 (37)
Neutropenic (n = 21)	–	2	14 (67)	5 (24)
Neutropenic non-alloSCT (n = 19)	–	2	12 (63)	5 (26)
Non-neutropenic (n = 9)	–	1	2 (22)	6 (67)
AlloSCT non-neutropenic (n = 7)	–	1	1 (14)	5 (71)

**These are considered as radiological lesions suggestive of IPA alloSCT; allogeneic hematopoietic stem cell transplantation.*

Thirteen patients (33.5%) were treated with c-AmB at a dose of 1 mg/kg/day. c-AmB was changed to ABLC (dose 3 mg/kg/day) in three patients and to liposomal AmB (dose 5 mg/kg/day) in one patient due to renal failure. Fourteen patients (36%) were initially treated with ABLC (dose 3–5 mg/kg/day) and 11 (28%) with liposomal AmB (dose 1-3 mg/kg/day). One patient was treated initially with oral itraconazole (dose 400 mg/day). The median duration of treatment was 18 days (range, 5-90 days). Fourteen patients received treatment with itraconazole after a median of 22 days (range, 7-90 days) of treatment with AmB. Two patients with hemoptysis underwent lobectomy, while sinus drainage was performed in the patient with sinusitis.

Outcome and causes of death

After treatment with any formulation of AmB, 12 (29%) patients achieved complete remission and four partial remission due to persistence of residual CT lesions. All of these four patients later achieved a complete remission (disappearance of residual lesions) during treatment with oral itraconazole. At the reference date of 31 December 2000, 32 patients had died. IPA was implicated in the patient's death in 24 (75%) cases: it was the only cause of death in 13 patients and was the primary cause of death associated with other causes in 11 patients (graft-versus-host disease = 8, progression of hematologic malignancy = 3). The median days from diagnosis to death from IPA was 7

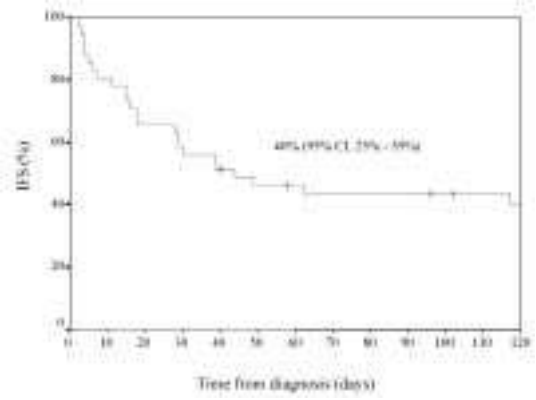

Figure 1. Infection-free survival of 41 hematologic patients with IPA.

days (range, 2-117). Eight deaths were not related to IPA and occurred at a median of 224 days after the diagnosis of IPA (range, 40 to 1,296). Nine patients were alive without any symptoms of IPA after a median of 165 days (range, 58-1,830).

Autopsy findings

Of the 24 patients whose death was IPA-related, autopsy was performed in 18 cases, and in 16 active invasive aspergillosis was found on microscopic examination.

Survival and prognostic factors

Those patients who did not fulfill the criteria of proven, highly probable or probable IPA during life were excluded from the survival analysis to avoid selection bias. Median follow-up after the diagnosis of IPA for the entire group is 42 days with a maximum follow-up of 61 months. Figure 1 illustrates the Kaplan-Meier survival curve for the whole population. The actuarial four-month infection-free survival was 40% (95% confidence interval [CI] 25% to 55%).

Univariate analysis

Twenty-two covariates were studied in univariate analysis (see statistical methods). Two factors were associated with prolonged survival: recovery of neutropenia during treatment ($p = 0.001$) and not having received an alloSCT ($p = 0.003$). Neutropenic status at diagnosis had no prognostic value in the whole patient series. However, among the 22 evaluable patients who were neutropenic at IPA, those who recovered from neutropenia during treatment had a better prognosis than those who did not recover (survival 86% vs 0%, respectively, $p = 0.002$). Variables with no impact on survival were CT findings, use of CT for diagnosis, interval from diagnosis to start of treatment, formulation of AmB used and prior use of prophylactic antifungals.

Multivariate analysis

The two variables found to be significantly related to survival in univariate analysis were entered into a multivariate analysis. A Cox regression model selected both variables as prognostic factors. Those patients who did not recover from neutropenia during treatment had a relative hazard of death of 10.5 (95% CI 2-53, $p = 0.005$) and those who

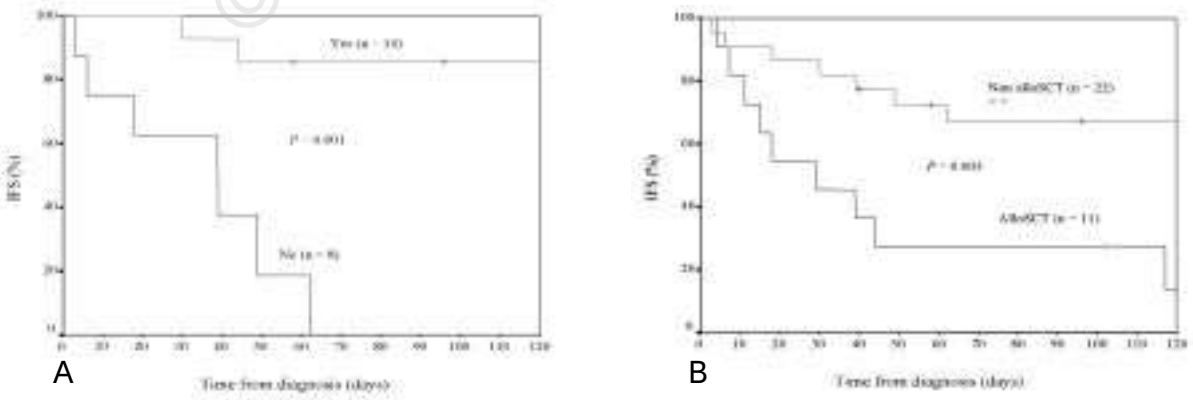

Figure 2. Infection-free survival (IFS) from diagnosis of IPA according to the two statistically significant variables in multivariate analysis. (A) IFS of 22 neutropenic patients according to neutrophil recovery after diagnosis. (B) IFS among alloSCT recipients and other patients.

received an alloSCT had a relative hazard of death of 3.4 (95% CI 1.2-12, $p = 0.04$). Figure 2 illustrates survival curves for these prognostic factors.

Discussion

The present descriptive study of IPA revealed that despite use of early thoracic CT scan and prompt initiation of antifungal therapy survival was 40%, and only 14% among alloSCT recipients. Our results are similar to those of previous studies[2-4,22] and confirm that IPA is a highly fatal opportunistic infection.

Our findings show that chest X-rays are not useful for the early diagnosis of IPA. Thirty-two percent of chest X-rays were normal, and only 8% were suggestive of IPA. CT scans are considered one of the most important procedures for the early diagnosis of IPA, and several authors showed that the use of early CT may improve survival.[8,23-25] These authors suggested that detection and characterization of lung infection by CT allows antifungal treatment to be started early and ultimately improves survival. Our results confirm the usefulness of CT scans. Ninety per cent of CT scans demonstrated lesions suggestive of IPA, and in 20 patients the CT scan was the first diagnostic procedure that suggested IPA.

Recovery from neutropenia also increased survival in our study. Prolonged neutropenia is a major risk factor for the development of IPA, and recovery from neutropenia has been shown to improve survival in various studies.[3,4,8,23,26-28] In our study persistent severe neutropenia after the first symptom or sign of infection adversely affected survival. Some authors suggested that the use of growth factors could improve the outcome of infection in neutropenic patients.[29] However, two recent studies[30,31] have not observed any statistically significant improvement in the outcome in relation to the use of growth factors. The relationship between granulocyte recovery and survival is especially relevant in non-alloSCT recipients, since in these patients development of IPA is usually related to later immunosuppression from GVHD.[5] Thus, 10/13 non-neutropenic patients who developed IPA were alloSCT recipients with GVHD.

In conclusion, better knowledge of the risk factors and clinical and radiological presentation of IPA allows for the early start of aggressive antifungal treatment.[32] However, despite early treatment, mortality from IPA is still high, and in our study two variables improved survival from IPA: neutrophil recovery during therapy and not having received an alloSCT.

Contributions and Acknowledgments

MS and RM were responsible for the conception and design of the study. MS collected and analyzed the data and wrote the manuscript. RM also contributed to the interpretation of the data and reviewed the final version of the manuscript. TF was responsible for the high resolution computed tomography procedures and CP for the bronchoscopies. AA, AS and SB collaborated in patient care and in preparation of the manuscript. JS is the head of the Division and critically corrected the different versions of the manuscript.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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Peer Review Outcomes

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Dr. Denis Caillot, who acted as an Associate Editor. The final decision to accept this paper for the publiaction was taken jointly by Dr. Caillot and the Editors. Manuscript received September 14, 2001; accepted March 13, 2002.

What is already known on this topic

IPA remains a life-threatening complication in neutropenic and allogeneic bone marrow transplanted patients. This study confirms the value of thoracic CT scan in diagnosing IPA.

What this study adds

This study enhances the value of the CT halo sign as an early indicator of IPA in neutropenic patients compared to allo-BMT patients in whom neutropenia has most often resolved at time of IPA occurrence.

Potential implications for clinical practice

The achievement of an early diagnosis of IPA needs the systematic use of thoracic CT scan in neutropenic patients (at risk of aspergillosis). Further studies in allogeneic BMT recipients are warranted to determine the optimal place of CT in this setting.

Denis Caillot, Associate Editor