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Results of a Multicenter Retrospective Study of a Combined Medical and Surgical Approach to Pulmonary Aspergillosis in Pediatric Neutropenic Patients

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Background. Invasive aspergillosis (IA) is a serious problem in patients suffering from hematological malignancies. Surgical resection has been reported to improve disease control and patient survival. There are few reports describing the role of surgery in children with pulmonary IA. ***Procedure.*** From October 1998 to September 2005, 21 patients fulfilled the inclusion criteria. Demographic and clinical data, as well as type and duration of antifungal therapy; surgery and related complications; time elapsing from surgery to resumption of chemotherapy were collected retrospectively through a specially designed form filled in by each investigator. ***Results.*** Eleven males and 10 females, aged between 2 and 17 years underwent one or more surgical lung resections for diagnostic and therapeutic purposes. Surgical complications were reported in three patients. Two patients, who underwent a wedge resection and a lobectomy, respectively, had no fungal lesions detected at surgery. Seventeen of 20 patients with malignancy resumed chemotherapy after a median of 19 days from surgery, range 7–81, and 11 of them underwent hematopoietic stem cell transplantation after a median time of 60 days from surgery, range 19–110. After a median follow-up of 1.7 years, 12 patients are alive while 9 patients have died from progression of their underlying disease. ***Conclusions.*** This study suggests that the combination of medical antifungal therapy and early surgical excision is a feasible and an effective strategy in pediatric patients with IA. In order to avoid unnecessary surgical procedures, we advise checking the response to antifungal therapy by chest-computed tomography immediately before the date of surgery. Pediatr Blood Cancer 2007;49:909–913. © 2006 Wiley-Liss, Inc.

Key words: aspergillosis; chemotherapy; invasive fungal infection; pediatric malignancy; surgery

INTRODUCTION

Invasive aspergillosis (IA) is a serious problem in patients with hematological or oncological malignancy, the mortality being as high as 40%–50% in patients after chemotherapy and 80%–90% in patients after hematopoietic stem cell transplantation (HSCT) [1,2]. The availability of safer formulations of amphotericin B, such as the lipid or liposomal formulation [3,4], and the recent introduction of new antifungal drugs, such as voriconazole and caspofungin, [5,6] has increased the therapeutic armamentarium against IA. New modalities of therapy, for example, high-dose liposomal amphotericin B [7], and the combined administration of antifungal drugs with synergistic mechanisms of action, may also improve the poor prognosis of patients with IA or infection by other filamentous fungi [8–11].

Despite these advances, antifungal therapy often fails to completely eradicate IA. Moreover, a prolonged treatment is required to maximize the response to IA, preventing the patient from maintaining the dose-intensity schedule of chemotherapy or delaying intensification with high-dose chemotherapy or HSCT. Several authors have reported that an aggressive surgical approach in adult patients with pulmonary IA has a beneficial impact on disease control and survival and is indicated both in the emergency situation for the prevention of massive hemoptysis and electively for resection of a residual mass [12–16]. However, there are only a few reports describing the role of surgery in children with pulmonary IA; and, most importantly, the time elapsing from diagnosis of IA to surgery and from surgery to resumption of chemotherapy has been inadequately analyzed.

We describe retrospectively the experience of five pediatric centers belonging to the Italian Association of Pediatric Hematology Oncology (AIEOP) which, in recent years, have combined early pulmonary surgery with antifungal therapy for IA. The main aims of the study were the evaluation of safety and efficacy of this combined approach in pediatric patients and impact of surgical intervention on the chemotherapy protocol.

MATERIALS AND METHODS

Patients eligible for the study had to meet the following criteria: be severely neutropenic pediatric hematological or oncological patients who had been diagnosed with suspected or documented pulmonary IA and who had undergone a surgical pulmonary resection as adjuvant therapy after initial systemic antifungal therapy. During the study period, from October 1998 to September 2005, 21 patients fulfilled the above criteria and were treated with a combined medical and surgical approach for pulmonary IA at the five participating AIEOP centers. Demographic and clinical data, as well as type and duration of antifungal therapy; surgery and related

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complications; time elapsing from surgery to resumption of chemotherapy were collected through a specifically designed form filled in by each investigator. Due to the retrospective nature of the study, the type of systemic antifungal therapy given before or after surgery was according to the policy of each center or at the discretion of the individual investigator. The follow-up data are as of March 31, 2006. The conduct of the study was approved by Ethics Committee of Hospital of Padua.

General Management of Patient With Suspected IA

The severely neutropenic patients were nursed in reverse-isolation or, for patients who had undergone HSCT, high-efficiency particulate-filtered air (HEPA) rooms, respectively. All centers used a standard recommended approach for the empiric treatment of fever based on broad-spectrum antibiotics and, for non-responding patients, amphotericin B or its lipid or liposomal formulation [17,18].

Definitions

The diagnosis and definition of IA was made according to published recommendations and international accepted criteria [19,20]. Severe neutropenia was defined by an absolute neutrophil count $<0.5 \times 10^9$/L. The response to antifungal treatment was defined as follows: complete response (CR) was the resolution of all clinical signs and symptoms attributable to IA and complete or very nearly complete radiographic resolution ($\geq$90%); partial response (PR) was a major improvement or resolution of the attributable clinical signs and symptoms and at least a 50% improvement in radiological signs; stable disease (SD) was consistent with some but less than 50% radiological improvement; and failure (F) was progression of, or death from, mycosis. Favorable (or major) response comprised both CR and PR [21]. Percentage, median, and range were used as appropriate to describe continuous and categorical variables, respectively. The Kaplan–Meier method was used to calculate the 3-month-survival probability (SAS Institute, Cary, NC, Version 8.2).

RESULTS

Details of the patient's demographic clinical characteristics are shown in Table I. There were 11 males and 10 females with a median age of 9.7 years. All but two patients, one with metastatic neuroblastoma and one with Kostmann syndrome (congenital neutropenia), were suffering from either acute lymphoblastic or acute myeloid leukemia. All episodes of IA started while the patients were severely neutropenic. Except for the patient with Kostmann disease, severe neutropenia followed the chemotherapy given as induction (1 patient), consolidation (12 patients), and relapse (7 patients) of the underlying disease. According to the criteria of Ascioglu et al., 9 and 12 patients were classified initially as probable and possible IA, respectively. All the patients with probable IA had a positive serum galactomannan test [22].

Eighteen patients had a single lung lesion while 4 patients had multiple lung lesions; of note, 3 patients had disseminated disease with involvement of central nervous system (CNS) and liver (2 patients) and of CNS, liver, and spleen (1 patient). One of these patients underwent excision of a cerebral aspergilloma located in the left parietal lobe after recovery from lung surgery.

Prior to surgery, 11 patients received amphotericin B or its lipid or liposomal formulation, or a triazole as mono-therapy for IA, whilst 10 patients received combination antifungal therapy with liposomal amphotericin B and voriconazole or caspofungin; or a

TABLE I. The Main Demographic and Clinical Characteristics of the 21 Patients Recruited Into the Study Are Shown

	Number
Sex (M/F)	11/10 (52%/48%)
Median age (years) at IA	10.4 years
Range	(1.2–17.2)
Underlying disease	
ALL	10 (48%)
AML	9 (43%)
Other	2 (9%); Neuroblastoma IV stage, 1; Kostmann disease, 1
Phase of treatment at diagnosis of IA	
Consolidation after CR	12 (57%)
Relapse	7 (33%)
Diagnosis of underlying disease	1 (5%)
Other	1 (5%) (Severe neutropenia in patient with Kostmann disease)
Organ involvement	
Lung	21
Single site	18 (86%)
Multiple site	3 (14%)
Other organs	3 (CNS and liver, 2; CNS, liver, and spleen, 1)
Type of antifungal therapy	
Monotherapy	11 (52%): d-AmB, 3; L-AmB, 6; ITR, 1; VOR, 1
Combination therapy	10 (48%): L-AmB + VOR, 2; L-AmB + Caspo, 4; Caspo + VOR, 4
Interval between the initial diagnosis of IA and surgery[a]	Median, 25 days; range 4–69

M, male; F, female; IA, invasive aspergillosis; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; NBL, neuroblastoma; CR, complete remission; CNS, central nervous system; d-AmB, deoxycholate-amphotericin B; L-AmB, liposomal amphotericin B; ITR, itraconazole; VOR, voriconazole; Caspo, caspofungin; [a]Considering only the 20 patients who underwent surgery within 3 months from diagnosis of IA.

combination of caspofungin and voriconazole. In this last group, 1 patient, who underwent lung surgery 213 days after the diagnosis of IA, was treated with the combination of caspofungin and voriconazole for 55 days and then maintained on voriconazole until the surgery. Apart from this patient, all the other patients underwent surgery early after the diagnosis of IA, the median interval to surgery being 25 days, range 4–69 (Table I).

Surgery

The main data regarding the surgery (type of surgery, hematological parameters, and surgery-related complications) are summarized in Table II. Given the fact that IA had not been proven before surgery in any patient, defining the diagnosis was one of the main indications for surgery in all patients. In particular, 3 patients (2 possible and 1 probable aspergillosis, respectively) underwent surgery despite a nearly complete radiological response, >90% of the initial pulmonary lesion, to remove the residual nodule before performing HSCT. In the others, apart from diagnosis, the indication for surgery was resection of a residual mass in patients with a partial response to antifungal treatment (16 patients) or in emergency situations such as prevention of massive hemoptysis (1 patient) and empyema (1 patient). All but one patient (a child affected by Down syndrome and acute myeloid leukemia) was scheduled for high-dose intensive chemotherapy or HSCT at the time of surgery.

Twenty elective surgical procedure were performed in 19 patients (one patient had a lobectomy 2 weeks after a previous wedge resection): 5 wedge-resections (4 on left superior lobe, 1 on right inferior lobe); 12 lobectomies (3 left upper, 4 left lower, 3 right upper, 1 middle, 1 right lower); 2 combined resections for multiple lesions: a middle lobectomy and a wedge resection of right upper and right lower lobe, respectively; finally, no resection was performed in 1 patient who started the surgical procedure with a thoracoscopy and then underwent a thoracotomy because no visible or palpable lesion could be detected.

The 2 patients who were operated on as an emergency for major hemoptysis and for empyema had a right lower lobectomy; and a wedge resection with toilet of the left hemithorax, respectively.

Overall, the surgery enabled the diagnosis of invasive fungal infection to be confirmed by histology and/or microbiology of lung tissue in 19 of 21 patients, as follows: *Aspergillus sp*. 15; *Mucor sp*. 2, *Aspergillus fumigatus*, 2. In the remaining 2 patients, who were classified as possible IA before surgery and who underwent a right lower lobectomy and thoracoscopy/thoracotomy, respectively, no documentation of fungal infection was found. Both patients had had a complete response to medical therapy before surgery, with reduction of chest CT lesions to less than 10% compared to those at the initial diagnosis.

No surgery related deaths occurred. Surgical complications were observed in 3 patients after elective surgery: 1 complete dehiscence of the surgical wound; 1 persistent thoracic effusion; and 1 pneumothorax which needed the positioning of a second drainage tube. After surgery, all patients were classified as complete responders from invasive fungal infection and were started on secondary antifungal prophylaxis (itraconazole or voriconazole). Overall, 17 of 20 patients with an underlying malignant disease resumed chemotherapy after a median time of 19 days from surgery, range 7–81, while 2 patients were withdrawn from chemotherapy for progression of underlying disease (they received only palliative cure) and chemotherapy was discontinued in 1 patient with Down syndrome and acute myeloid leukemia. Eleven of these 17 patients underwent HSCT at a median time of 60 days from surgery, range 19–110. The 21st patient, affected by Kostman disease, underwent HSCT after 223 days from surgery. Notably, no evidence of infection by *Aspergillus* or *other filamentous fungi* was found in all patients at work-up assessment performed before HSCT.

TABLE II. The Main Characteristics of Surgical Operation in Patients With IA

	Number
Reason for surgery	
Elective	Diagnosis, 3
	Partial response, 16
Emergency	Hemoptysis, 1; empyema, 1
Type of resection	
Elective	[a]Wedge resection, 5;
	[a]Lobectomy, 12
	Combined (lobectomy + wedge resection), 2
	No resection, 1
	Lobectomy, 2
Emergency	Lobectomy, 1
	Wedge resection, 1
Hematological parameters before surgery	
Neutrophil ($\times 10^9$/L)	Median 3.2; range 0.4–2.1
Platelets ($\times 10^9$/L)	Median 186; range 60–683
Complications	Pneumothorax, 1
	Persistent pleural effusion, 1
	Dehiscence of wound, 1
Time to resumption of chemotherapy[b]	Median (days) 19, range 7–81
Time to HSCT[c]	Median (days) 60, range 19–110

[a]One patient underwent both a lobectomy and wedge resection separately; [b]Only for 17 patients who resumed intensive chemotherapy; [c]Only for the 12 patients who underwent stem cell transplantation.

Follow-Up and Outcome

Nineteen of the 20 patients who had early surgery, were alive at 3 months after the development of pulmonary fungal infection whilst one patient died of progression of their underlying disease. The 3-month-survival probability was 95%, CI 85–100. Two of 21 patients had a new episode of invasive fungal infection after surgery in a different site from the original one: 1 probable pulmonary aspergillosis and fusarium sepsis after 101 and 249 days from surgery, respectively. Both patients had had a previous relapse of underlying disease that occurred 16 and 133 days after allogeneic and autologous HSCT, respectively. After a median follow-up of 1.7 years, range 0.3–7, 12 of 21 (43%) are alive whilst 9 patients have died. The main cause of death in all patients was progression of the underlying malignant disease.

DISCUSSION

Invasive fungal infections by *Aspergillus sp*. or other molds are increasingly reported in hematological patients and continue to represent a life-threatening complication despite the introduction of new antifungal drugs [23,24]. Although the diagnosis of IA is still a challenge in the daily management of a neutropenic patient, achieving the correct etiologic diagnosis is crucial to prescribing (or administering) the most appropriate therapy. In this study, surgery enabled confirmation of the diagnosis in 19 of 21 patients either by histopathological examination or by microbiological culture of lung tissue. Interestingly, *Mucor sp.* resulted the etiologic agent of 2 pulmonary fungal infections classified before surgery as possible IA. In the remaining 2 patients, none of the lesions described on the chest CT scan done 1–2 weeks before surgery were detected during operation. We presume that these patients achieved a complete response to antifungal therapy during the interval between the last CT scan and surgery. For this reason, we advise checking the response to antifungal therapy by CT scan immediately before the date of surgery.

In the last decade, it has been demonstrated that the systematic use of thoracic CT scans combined with surgical resection of pulmonary lesions, has reduced the mortality due to invasive pulmonary aspergillosis from 41% to 14% [19]. In a retrospective study, the patients with localized pulmonary aspergillosis treated with both antifungal drugs and early lung resection, compared to patients treated only with antifungal drugs, showed a reduced progression of fungal disease at 6 months and a better overall survival: 17% versus 52% and 70% versus 42%, respectively [15]. These results are explained by the fact that surgical resection gives superior local control of infection compared to antifungal therapy alone, especially in the case of a large mass; surgery also permits an accurate diagnosis indicating the optimum treatment needed; and finally, surgery can prevent death due to massive hemoptysis which may occur early in the course of infection as the patient recovers from neutropenia [25,26].

To date, data on pediatric patients are limited to small case series [27–30]. Combined medical-surgical therapy for pulmonary IA is clearly advocated by Gow et al. who recently reported a favorable outcome for 4 out of 18 patients who had been operated on, while no survivors were observed among 25 children treated with medical therapy alone. Moreover, in the 27 patients who underwent HSCT, the outcome was better if transplantation occurred after treatment of invasive pulmonary aspergillosis rather than before [27]. Nevertheless, the post-surgical complications, the timing of surgery, and the time to resumption of chemotherapy or to HSCT with respect to the diagnosis of IA and date of surgery have been not adequately described so far in pediatric patients.

The timing of surgery after the diagnosis of IA has been a key-issue of this study. Apart from 1 patient who was operated on 213 days after developing pulmonary IA, in order to remove a residual nodule before undergoing a HSCT from a mismatched unrelated donor, the other 20 patients were operated on early after developing IA, at a median interval of 25 days. The aims of surgery were to define the diagnosis and to eradicate the residual lesions after initial full-dose antifungal therapy with one or more active drugs.

A crucial point of surgery for pulmonary IA is represented by post-operative complications which can delay the prompt resumption of chemotherapy. In this study, complications related to surgery were diagnosed in only 3 of 22 (14%) surgical procedures; these were minor and managed with standard supportive measures. Yeghen et al. [16] reported post-operative complications in 9 of 26 adults, (35%) patients who developed IA before HSCT. More importantly, no complication in our series was fatal despite the fact that myeloid recovery was still suboptimal in some patients at the time of surgery. Other authors have previously reported an early post-operative mortality rate of between 5% and 39% [12,19,31,32]. Moreover, in our series of patients, chemotherapy was resumed early after a median interval of 19 days from surgery and, in the eligible patients affected by malignancy, an autologous or allogeneic HSCT was performed at median time of 60 days from surgery. Overall, a very encouraging 3-month survival figure of 95% was achieved; and 12 of 21 patients are alive after a median follow-up of 1.7 years.

Interestingly, both episodes of IA that occurred after surgery, followed the relapse of the underlying hematological disease. This fact confirms the importance of the patient's remission status in maintaining the results achieved with the best medical and surgical therapy for IA.

In all cases conservative surgical procedures were performed. Most patients underwent lobectomy because the fungal lesions were localized deep in the lung, whilst resection was limited to a wedge resection in less than 30% of cases. Nevertheless, we believe that wedge resections, via a thoracotomy or a thoracoscopy, represent good operative options especially when imaging investigations indicate that the lesions are superficial, multiple, or bilateral [27,33].

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