RISK OF REACTIVATION OF A RECENT INVASIVE FUNGAL INFECTION IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES UNDERGOING FURTHER INTENSIVE CHEMO-RADIOTHERAPY. A SINGLE-CENTER EXPERIENCE AND REVIEW OF THE LITERATURE

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Abstract

Background. Patients with hematologic malignancies and a history of an invasive fungal infection are considered to be at high risk of suffering reactivation of the infection during subsequent intensive chemotherapy.

Patients and Methods. From January 1993 to September 1996, nine patients with a hematologic malignancy and previous invasive pulmonary aspergillosis (IPA) or *Pseudallescheria boydii* pneumonia and five with invasive candidiasis received further intensive chemotherapy (n=3) or a bone marrow or peripheral blood stem cell transplant (n=11) four days to 13 months (median three months) from the start of therapy for the fungal infection. Five patients with IPA and all five with invasive candidiasis showed complete or good partial radiologic resolution of the infection with the primary antifungal therapy given, which was continued before, during and after the period(s) of subsequent neutropenia.

Results. Twelve of the 14 patients showed no signs of progression or reactivation of the fungal infection during therapy, while two patients with active IPA died of progressive aspergillosis shortly after an allogeneic transplant. A review of the literature revealed that in both types of infections the risk of reactivation and dissemination appears low after achieving clinical and radiologic signs of response, which takes several weeks or months before proceeding to further antileukemic therapy.

Interpretation and Conclusions. Despite a lack of definite evidence, administration of an active antifungal drug before, during and after the period of neutropenia apperas to be useful. In IPA residual masses, nodules or cavities in the lung usually contain viable invasive fungal elements and should be resected whenever possible. On the other hand, the risk of reactivation and progression of an active fungal infection during intensive chemo-radiotherapy is very high, and novel therapeutic strategies seem to be warranted in this setting.
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Key words: aspergillosis, candidiasis, reactivation, chemotherapy, transplantation

Treatment of many hematological malignancies requires several consecutive cycles of myelotoxic chemotherapy (CHT), often followed by peripheral blood stem cell (PBSCT) or bone marrow (BMT) transplant after intensive chemo-radiotherapy. Invasive fungal infections (IFI) are a frequent complication of intensive chemotherapy for acute leukemias and salvage protocols for the chronic leukemias or lymphomas.[1,2] Although they can be successfully managed with antifungal therapy and recovery of the neutrophil count, the causative fungi may remain in the infected tissues and the classic study by Robertson *et al*.[3] confirmed that these infections can reactivate during successive courses of chemotherapy causing full-blown invasive disease.

Although there have been many reports of successful continued intensive chemotherapy,[4-6] or PBSCT/BMT[7-16] in patients with a previous IFI, some authors are still concerned that the risk of reactivation might be high and that special antifungal prophylaxis should be given in this situation.[3,17-21] We report the results of a prospective management strategy for such patients used in our institution since early 1993. Additionally, we review the currently available literature and make management recommendations for these patients.

Patients and Methods

Patients

From January 1993 to September 1996 a total of 17 patients with a previous IFI were candidates for further intensive CHT or a BMT/PBSCT according to the protocols for their specific underlying malignancy, and 14 of them eventually received such treatment.

Eleven patients with an acute leukemia (n=9) or high-grade lymphoma (n=2) who had developed an IFI after a cycle of intensive CHT given as induction, consolidation or salvage therapy received further intensive CHT until completing the full treatment plan. Three other patients with aplastic anemia or

acute leukemia developed an IFI just before receiving a PBSCT or BMT. Eight patients developed an invasive pulmonary aspergillosis (IPA), five developed an invasive candidiasis and one pneumonia due to *Pseudallescheria boydii*. Details on the patients' characteristics, treatment given and response are shown in Table 1.

Four patients with aspergillosis were considered as having a probable IPA as defined by isolation of an Aspergillus species in sputum or bronchoalveolar lavage samples and radiologic evidence consistent with IPA during the pancytopenic phase after CHT.[3,22] Additionally, three patients had a *definite* IPA since, besides the above criteria, a biopsy specimen showed tissue invasion by septated branching hyphae, and one only had radiologic evidence suggestive of an IPA in the specific clinical context and was considered as having a *possible* IPA.[3,22]

All patients with invasive candidiasis and one with *Pseudallescheria boydii* pneumonia had a definite deep-tissue infection. The patient with *Pseudallescheria boydii* pneumonia had a lobar pneumonia with a positive bronchoalveolar lavage (BAL) for the microorganism, lack of response to antimicrobials and amphotericin B and response to itraconazole.

Four patients had a clinical-radiological picture typical of chronic systemic candidiasis (CSC) together with positive cytology for yeasts (n=3) or a positive culture (n=1) of the material obtained from a fine needle aspirate of a liver or splenic nodule.

The patient with pulmonary candidiasis had a positive transbronchial biopsy for yeasts and pseudohyphae and a positive BAL for *Candida albicans*. Characteristics of individual patients are detailed in Table 1.

Antifungal treatment protocol

Primary treatment for the IFI included amphotericin B deoxycholate (AmB) at a daily dose of 0.6 to 0.8 mg/kg in three cases of candidiasis and 1.0 to 1.3 mg/kg in four cases of aspergillosis. Liposomal AmB at a dose of 3 to 5 mg/kg/day was used in three aspergillosis, fluconazole (200-400 mg/day iv or po) was used in all cases of candidiasis and itraconazole (400 mg/day po) in three cases of aspergillosis and the patient with *Pseudallescheria boydii* pneumonia. Fluconazole (FCZ) or itraconazole (ICZ) were given after obtaining an initial response to AmB in five cases, as seen in table 1 (patients #4, 9, 10, 11, 12). One patient underwent lobectomy to remove a residual mass before proceeding to an allogeneic BMT (patient #1), and the resected specimen showed evidence of IPA.

This prospective management protocol was begun in January 1993. All consecutive patients with a probable or definite IFI were to receive further CHT or PBSCT/BMT if they had shown signs of clinical and radiological improvement with the primary antifungal therapy.

The same primary therapy to which the patient had responded was to be continued all throughout the CHT or PBSCT/BMT and for at least three months from the completion of the antineoplastic treatment. This *secondary prophylaxis* FCZ was given at a dose of 200 mg/day and ICZ at a dose of 200 mg/12 hrs depending on the type of fungal infection (see Table 1). Both were initially administered orally, yet successively FCZ was switched to the intravenous route and ICZ to AmB (0.5 mg/kg/day) if mucositis, vomiting or diarrhea prevented oral intake; this eventually occurred in five of the ten patients who underwent PBSCT/BMT.

Additionally, FCZ or ICZ were to be changed to AmB (0.5 mg/kg/day) if the patient suffered persistent neutropenic fever of unknown origin for at least five days in keeping with the standard policy of early empiric broad-spectrum antifungal therapy in neutropenic patients with prolonged fever. No patient received concomitant treatment with AmB and FCZ or ICZ. Following resolution of the fever and the neutropenic episode, the original antifungal (FCZ or ICZ) was to be restarted and continued for at least three months.

Literature search

All the available literature on this subject was found through a MEDLINE data base search from 1982 until March 1996, selecting all articles on continued antineoplastic treatment in patients with previous fungal infections and leukemia, lymphoma and PBSCT/BMT. Additional studies were identified by

careful bibliographic review of these articles. Four of the patients included in this report have been previously reported and will thus not be included in the literature review.[7,8]

Results

Five of the nine patients with previous IPA or *Pseudallescheria boydii* pneumonia had complete resolution of clinical and radiologic signs of the infection before proceeding to the next course of CHT (n=1) or BMT/PBSCT (n=4), while four had evidence of active IPA at CHT (n=1) or BMT/PBSCT (n=3). The time interval from the diagnosis of the IPA to the next course of CHT or the PBSCT/BMT ranged from 4 days to 13 months, with a median of four months.

Two patients died early after an allogeneic PBSCT with progressive IPA, and both had active infection before the transplant (patients #7 and 8). One died early after salvage CHT for leukemia with no evidence of aspergillosis on postmortem examination (#3). None of the other cases showed signs of progression of the aspergillosis during their treatment, including the other two patients with active IPA at CHT or BMT, with computerized tomography (CT) scans showing only residual scars two to three months after completing therapy. The six patients with IPA who survived the CHT suffered a median of 45 days (range 30-72 days) of neutropenia (neutrophil count $< 0.5 \times 10^9$/L) during the following courses of CHT. Granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage CSF (GM-CSF) were given in all cases following CHT or BMT to hasten neutrophil recovery.

All six patients eventually died from their underlying malignancy (n=3), graft-versus-host disease and cytomegalovirus pneumonitis after BMT (n=1), bacterial sepsis (n=1) or idiopathic interstitial pneumonitis after BMT (n=1). The median time from the last course of CHT or BMT until death was six months (range 3-18), and *post mortem* examinations were done in four cases, with no evidence of active IPA.

The five patients with hepatosplenic candidiasis or CSC (n=4) and pulmonary candidiasis (n=1) responded clinically to their primary therapy. Most of them, however, had residual lesions in liver and/or spleen on CT examinations performed before subsequent CHT (n=1) or BMT/PBSCT (n=4), but none showed clinical or radiologic signs of progressive infection. These patients suffered a median of 21 days (range 17-50) of neutropenia and all received G-CSF or GM-CSF after every course of CHT or BMT. Two patients died of leukemic relapse and one from chronic graft-versus-host disease seven to 24 months from the last treatment. The other two are alive and disease-free nine and 18 months from the last CHT or BMT/PBSCT, and all radiologic abnormalities had disappeared at three months. Again, the time

Table 1. Patient characteristics.

Pat. no.	Age/ Sex	CHT previous to IFI	Diagnosis	Type of IFI and species	Primary antifungal Tx	Type of later CHT/BMT	Interval from Dx of IFI to later CHT/BMT (mo)	Status of IFI at CHT/BMT	Antifungal Px given during CHT/BMT	Total duration of neutropenia after CHT/BMT (days)	Final outcome
1	16/M	BMT salvage CHT	ALL 2nd relapse	definite IPA *Aspergillus fumigatus*	AmB + lobectomy*	2nd BMT	5	CR	ICZ	30	Died on day +109 of GVHD
2	27/F	salvage CHT	ALL	probable IPA *Aspergillus fumigatus*	AmB	ABMT	4	CR	ICZ	45	Died from relapsed ALL at 12 mo.°
3	66/M	salvage CHT	AML	definite IPA *Aspergillus fumigatus*	ICZ	salvage CHT	13	CR	ICZ	21	Died from hepatotoxicity on day 21 °
4	71/M	induction CHT	AML	probable IPA *Aspergillus sp.*	AmB + ICZ	reinduction + consolidation CHT	4 days 2 mo.	active CXR and CT lesions	ICZ	72	CXR normalized at 3 mo. Died from relapsed AML at 4 mo.°
5	21/M	immunosuppressive therapy	aplastic anemia	possible IPA	AmB	BMT	1	active CT lesions	ICZ	24	CT normalized at 2 mo. Died from IP at 6 mo.
6	39/M	consolidation CHT	AML	*Pseudallescheria boydii* pneumonia	ICZ	ABMT	12	CR	ICZ	45	Died from relapsed AML at 18 mo.°
7	34/M	salvage CHT	AML	probable IPA *Aspergillus sp.*	liposomal AmB	PBSCT	1	active CT lesions	liposomal AmB	7	Died on day +7 of HVOD and progressive aspergillosis
8	48/F	immunosuppressive therapy	aplastic anemia	definite IPA *Aspergillus fumigatus*	liposomal AmB	PBSCT	1	active CXR and CT lesions	liposomal AmB	9	Died on day +9 of progressive aspergillosis
9	48/M	consolidation CHT	AML	probable IPA *Aspergillus sp.*	AmB + ICZ	PBSCT	2	CR	ICZ	15	Died at 3 mo. from bacterial sepsis°
10	44/M	consolidation CHT	AML	*Candida albicans* pneumonia	liposomal AmB + ICZ	BMT	3	CR	FCZ	17	A+W at 11 mo.
11	43/M	induction CHT	AML	CSC Cytology only#	AmB + FCZ	ABMT	5	improvement of CT lesions	FCZ	50	CT normalized at 3 mo. Died from relapsed AML at 7 mo.°
12	18/M	induction CHT	lymphoblastic lymphoma	CSC Cytology only#	AmB + FCZ	salvage CHT + ABMT	6	improvement of CT lesions	FCZ	40	CT normalized at 6 mo. Died from relapsed ALL at 24 mo.
13	50/F	salvage CHT	ALL	CSC Cytology only#	FCZ	PBSCT	25	improvement of CT lesions	FCZ	21	CT normalized at 5 mo. Died from chronic GVHD at 12 mo.°
14	29/M	consolidation CHT	Burkitt's lymphoma	CSC *Candida glabrata*#	FCZ	consolidation CHT	1	improvement of CT lesions	FCZ	21	A+W at 20 mo. CT normalized at 3 mo.

CHT, chemotherapy; IFI, invasive fungal infection; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; IPA, invasive pulmonary aspergillosis. Definite, probable and possible as defined in text; CSC, chronic systemic candidiasis; Tx, treatment; Px, prophylaxis; AmB, amphotericin B; ICZ, itraconazole; FCZ, fluconazole; BMT, allogeneic bone marrow transplant; ABMT, autologous bone marrow transplant; PBSCT, allogeneic peripheral blood stem cell transplant; CT, computerized tomography scans; CR, complete remission or only residual scaring on CT examination; GVHD, graft-versus-host disease; HVOD, hepatic venocclussive disease; IP, interstistial pneumonitis; A+W, alive and well. *Material obtained from a fine needle aspiration of hepatic and/or splenic nodules. *Histologic evidence of IPA in the resected tissue. ° No evidence of invasive fungal infection at postmortem examination.

Table 2. Reported cases of continued chemotherapy and/or BMT in patients with previous chronic systemic candidiasis.

Author (year)	# pts.	Underlying diseases	Primary antifungal Tx	Type of later CHT/BMT	Interval from Dx of CSC to later CHT/BMT	Status of fungal infection at CHT/BMT	Antifungal Px given during CHT/BMT (AmB,mg/kg/day)	No. reactivations of candidiasis	Total duration of antifungal Tx after CHT/BMT	Final outcomes
Von Eiff [17] (1990)	5	AML	AmB + 5-FC	salvage CHT (n=4) BMT (n=1)	medium 9 mo. (range 5-11)	normal or improved CT	none	5/5	–	all 5/5 died of disseminated candidiasis
Kauffman [9] (1990)	2	AML	FCZ	BMT	3 and 7 mo.	Normal CT	NS	0/2	NS	NS
Tanaka [10] (1992)	1	AML	AmB + miconazole	2nd BMT	12 mo.	reactivation of CT lesions	AmB (0.5) + FCZ	0/1	NS	alive and well at 24 mo.
Dear [18] (1994)	1	AML	AmB + 5-FC	consolidation CHT	6 mo.	improved CT	AmB (0.5)	1/1	1.5 mo.	CNS candidiasis 1.5 mo. later.
Bjerke [11] (1994)	15	AML (n=9) ALL (n=1) CML (n=1)	AmB (n=15) + FCZ (n=3)	BMT (n=13) ABMT (n=2)	median 3 mo. (range 0.5-7)	normal CT (n=4) improved CT (n=9) progression on CT (n=2)	none (n=4) AmB (0.5) (n=7) AmB (0.5) + 5-FC (n=4)	3/15 died with disseminated candidiasis and aspergillosis*	NS	7/15 died < 100 days, 3 with fungal infection. 5/15 died of relapsed leukemia> 100 days.
Katayama [19] (1994)	2	AML	AmB + FCZ	BMT (n=1) ABMT (n=1)	4 and 6 mo.	improved CT	NS	1/2	6 mo.	1 reactivation of CSC which responded to further AmB + FCZ.

*CHT, chemotherapy; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; CSC, chronic systemic candidiasis; Tx, treatment; Px, prophylaxis; AmB, amphotericin B; ICZ, itraconazole; 5-FC, 5-flucytosine; FCZ, fluconazole; BMT, allogeneic bone marrow transplant; ABMT, autologous bone marrow transplant; CT, computerized tomography scans. *2/3 disseminated candidiasis were due to a different species of Candida than isolated pre-BMT.*

elapsed from the diagnosis of the IFI to the next course of CHT or BMT/PBSCT varied a lot, with a median of three months (range 1.5-6).

In both IPA and CSC patients, this parameter turned out to be a balance between the time required to obtain a clinical and radiologic response of the infection (as stated in the management protocol) and the urgency for further antineoplastic therapy.

Discussion

The literature search identified 12 reports of IPA or other mold infections[3-8,12-16,21] and six of CSC[9-11,17-19] in patients later receiving further CHT or BMT. There are a total of 26 cases of CSC, mostly as small single-center experiences.[9-11,17-19] Table 2 summarizes the six reports. Most of the patients had acute leukemia, as seen in our experience.

The largest report is from the Seattle group who analyzed 15 consecutive patients with a previous CSC who received an allogeneic BMT (n=13) or autologous BMT (n=2) during a 20-month period.[11] All of the patients had a definite CSC and were treated with AmB. During BMT AmB was used as continued treatment or prophylaxis in 11 cases with residual (n=9) or progressive (n=2) CT lesions, with (n=4) or without additional 5-flucytosine, and the remaining four patients received no antifungal prophylaxis since they had no residual CT lesions. Following BMT there were three cases of fatal acute disseminated candidiasis, but the same species was only involved in one case, while another species was iso-

lated in two other cases which was probably resistant to the antifungal agent used. Twelve cases showed no evidence of reactivation of CSC or other yeast infection, but there were only three long-term survivors due to later leukemic relapses or procedure-related mortality. Interestingly, of the only two patients who had recently-diagnosed (immediately pre-BMT) CSC and progressive hepatosplenic lesions, one died on day 33 of the procedure with disseminated candidiasis despite receiving high-dose AmB+5-flucytosine.

The other five reports[9,10,17-19] include a total of 11 patients with previous CSC, seven of whom had a reactivation of the infection following CHT or BMT, despite the fact that many had normal or resolving CT scans when they received further antileukemic therapy four to 12 months later (see Table 2), and one received prophylaxis with AmB during this period. These single or small case reports, however, should be interpreted with caution, since they can represent either a positive or a negative reporting bias.

On the other hand, prospective consecutive series of patients with a homogeneous management strategy, such as our experience or the Seattle report,[11] probably give a better idea of the actual risk involved, which appears to be low in patients in whom enough time has elapsed between the diagnosis of the CSC and subsequent intensive CHT and whose infection has clearly responded clinically and radiologically. The need for targeted antifungal prophylaxis in such cases appears warranted since in

Table 3. Reported cases of continued chemotherapy and/or BMT in patients with previous invasive pulmonary aspergillosis.

Author (year)	# pts.	Types of infections	Underlying diseases	Primary antifungal Tx	Type of later CHT/BMT	Interval from Tx to later CHT/BMT	Status of fungal infection at CHT/BMT	Antifungal Px given during CHT/BMT (AmB, mg/kg/day)	Num. reactivations of aspergillosis	Total duration of antifungal Tx after CHT/BMT	Final outcomes
Robertson [3] (1988)	12	IPA	AML	AmB	consolidation CHT	NS	NS	none	9/12	–	final outcomes of the 9 reactivations NS
Schattenberg [12] (1988)	1	definite IPA	AML	AmB + 5-FC + lobectomy	consolidation CHT + BMT	1 mo.	CR	ICZ	0/1	2 mo.	alive and well at 14 mo.
Karp [4] (1988)	10	definite IPA	AML	AmB + 5-FC	consolidation CHT	median 2 mo. (range 1-4)	PR (n=5) CR (n=5)	none (n=1) AmB (1.0) + 5-FC (n=9)	3/10*	until GRAN recovery	1/10 died of IPA° 2/10 whose IPA progressed responded to further antifungal therapy. 7/10 showed no signs of reactivation (5/5 in CR and 2/5 in PR)
Lupinetti [13] (1992)	2	1 Fusarium sp. pneumonia and 1 definite IPA	ALL	AmB + bilateral segmentectomies	BMT	2 mo.	NS	none	0/2	–	died from other causes without fungal infection.
Richard [14] (1993)	8	6 definite and 2 probable IPA	AML(n=7) ALL(n=1)	AmB(n=8) + ICZ (n=1) + surgical resection (n=3)	consolidation CHT (n=4) ± ABMT (n=6) or BMT(n=2)	median 5 mo. (range 3-8)	NS	AmB (0.5)	0/8	until GRAN recovery	4/8 died of other causes 4/8 were alive and well at 8-23 mo.
McWhinney [15] (1993)	7	all definite IPA	AML(n=4) ALL(n=3)	AmB(n=7) + surgical resection (n=6)	BMT	mean 2 mo.	NS	AmB (0.25-0.5)(n=5) ICZ (n=1) none (n=1)	0/7	NS	3/7 died of other causes 4/7 were alive and well at 11-60 mo.
Cowie [5] (1994)	3	2 definite IPA 1 Aspergillus sinusitis	AML(n=2) lymphoma (n=1)	AmB(n=3) + ICZ (n=2) + lobectomy (n=1)	ABMT(n=2) consolidation CHT(n=1)	NS	CR	ICZ (n=2) AmB (0.5)(n=1)	0/3	2,6,6 mo. (ICZ only)	1/3 died of other cause 2/3 are alive and well at 3 and 4 years
Nosari [6] (1994)	4	all probable IPA	AML	ICZ(n=4) + AmB(n=3)	BMT(n=1) consolidation CHT (n=3) ± ABMT(n=2)	NS	CR	ICZ	0/4	until GRAN recovery	2/4 died of other causes 2/4 were alive and well at 4 and 11 mo.
Levy [21] (1996)	1	IPA and mucormycosis	ALL	AmB + surgical resection	BMT	2 mo.	PR	NS	1/1	–	died of disseminated aspergillosis
Michailov [16] (1996)	7	1 probable IPA 6 possible IPA	AML	AmB(n=7) + ICZ(n=4)	consolidation CHT(n=6) ± ABMT(n=7)	median 6 (range 3-21)	CR	AmB (0.5-1) + ICZ	0/7	3 mo. (ICZ only)	4/7 died of other causes 3/7 were alive and well at 8,9,57 mo.

CHT, chemotherapy; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; CSC, chronic systemic candidiasis; Tx, treatment; Px, prophylaxis; AmB, amphotericin B; ICZ, itraconazole; 5-FC, 5-flucytosine; FCZ, fluconazole; BMT, allogeneic bone marrow transplant; ABMT, autologous bone marrow transplant; CT, computerized tomography scans. *2/3 disseminated candidiasis were due to a different species of Candida than isolated pre-BMT.

one report all five patients with an adequately treated CSC five to 11 months earlier had a fatal disseminated candidiasis during later CHT/BMT without the use of any prophylaxis.[17]

Ten articles which include 55 patients with a previous IPA or another invasive mold infection were found through the literature search.[3-6,12-16,21] Table 3 summarizes these reports.

Nearly all patients had an acute leukemia and developed the infection after intensive CHT, as in our own experience and in the patients with CSC. This is of course consistent with the predominance of fungal infections in acute leukemia patients and after BMT.[1,2]

The earliest reports did not specify the status of the fungal infection before subsequent CHT and showed a very high rate of fatal reactivations of the fungal infections,[3,20] contributing to the generalized impression of the high risk involved.

In the report by Viollier et al.[20] 21 acute leukemia patients developed Aspergillus sinusitis during intensive chemotherapy and 18 were successfully treated with AmB. Eleven of these patients (61%) had relapses and dissemination of their Aspergillosis during subsequent CHT, close to the 75% rate of reactivation reported by Robertson et al.[3] The former report, however, is not included in Table 3 since no further details were given to better interpret their findings. As seen in Table 3, ANB was mostly given as primary therapy for IPA, although ICZ has been increasingly used over the last three years. Surgical resection of residual large lung cavities or nodules before further intensive CHT was done in 14 cases, and, as in our patient #1, histological examination of the resected tissue always showed residual invasive hyphal elements, indicating the presence of viable fungi. Thirty-one patients went on to receive a BMT while the other 24 received one or more cycles of intensive consolidation CHT for their acute leukemia. The time elapsed from the diagnosis of the IPA to the next course of CHT or BMT/PBSCT varied a lot, and, as in our experience and in the patients with previous CSC, probably depended on the time required to obtain a clinical and radiologic response of the infection and the urgency for further antineoplastic therapy. Most importantly, however, was the fact that most cases had either shown a complete resolution or only residual scars were seen on CT examinations performed pre-CHT or pre-BMT, and this probably indicates the presence of little, if any, viable invasive fungal elements. None of these patients showed signs of reactivation of the pulmonary infection after CHT or BMT, whether AmB alone, AmB + 5-flucytosine and/or ICZ were used as prophylaxis during and after therapy, as seen in our experience.

Not enough details were given in three reports[3,20,21] that included a total of 31 acute leukemia patients

with previous Aspergillosis; although 21 of these patients showed fatal reactivations/disseminations of their infection early during therapy, the lack of details regarding the response to previous antifungal therapy, the status of the infection prior to further intensive CHT or the antifungal prophylaxis given precludes the development of any definite conclusions, but it seems reasonable to assume that when not properly under control or when significant radiologic abnormalities persist and without antifungal prophylaxis, these infections do disseminate rapidly during subsequent intensive CHT or BMT.

Particularly interesting is the report by Karp et al.[4] who used high-dose AmB with 5-flucytosine as antifungal prophylaxis during subsequent courses of intensive CHT in 9/10 patients with acute myelogenous leukemia and previous IPA. Despite this aggressive antifungal prophylaxis, 3/5 patients with only partial resolution of the CT lung lesions before CHT showed progression of the fungal infection during neutropenia, proving fatal in the only patient who received no prophylaxis. In contrast, none of the five patients with only residual CT abnormalities showed signs of progression.

As stated above, the presence of significant radiologic abnormalities was associated with histologic evidence of IPA in the 15 cases who had a surgical resection of residual lung lesions before receiving further therapy, and this may explain the high rate of reactivation and dissemination in this site. Thus, in our opinion the risk of reactivation of an IPA is low in patients in whom enough time has elapsed between diagnosis and subsequent intensive CHT and when the infection has clearly responded clinically and radiologically. Although AmB has been traditionally considered the drug of choice in the treatment of IPA, ICZ has been shown to be very effective and less toxic in treating this condition.[38] Thus, it seems to be an interesting alternative for secondary prophylaxis, and the seven cases who received this agent in our series as well as other reports[5,6,21] support this hypothesis. ICZ, however, has an erratic gastrointestinal absorption in patients with mucositis, and thus it should be used both for treatment and prophylaxis when the serum levels can be monitored.[38] Unfortunately, none of the patients reported herein had ICZ serum levels checked due to unavailability of the test at the time of treatment.

Despite the fact that the risk of fungal reactivation is well known, large studies on prophylactic strategies for preventing fungal infections in leukemia patients or during BMT have not specified the number of patients, if any, with a previous fungal infection.[24-26] Furthermore this variable has not been analyzed in large studies aimed at describing the risk factors for developing an invasive fungal infection after BMT.[27,28] This, of course, would have been very useful in calculating the actual risk of

reactivation.

In the absence of such data, we believe the best objective results come from analyzing series of consecutive patients with a homogeneous management strategy, as is the case of the Seattle report of CSC[11] and four of the reports on IPA.[4,14-16]

For other less common invasive fungal infections, the risk of reactivation and dissemination during subsequent CHT is unknown. Fusariosis has been reported to reactivate and disseminate during later CHT,[29] and one of the authors of the current report (R.M.) has observed a fatal reactivation and dissemination of a fusariosis during an allogeneic PBSCT that had been apparently successfully treated three months earlier. Very little, if anything, is known about other infections such as cryptococcosis, *Pneumocystis carinii* pneumonia,[30] or other pathogens who have a known tendency to reactivate in other settings, mainly in patients with the acquired immunodeficiency syndrome, unless long-term secondary prophylaxis is given.[31-33] It seems reasonable, however, to consider such patients at risk for reactivation and to apply adequate prophylaxis before, during and after CHT for their leukemia or BMT/PBSCT.

In conclusion, hematologic patients with a previous history of an invasive fungal infection can safely receive further intensive CHT and even proceed to BMT/PBSCT (allogeneic or autologous) provided that there are clinical and radiologic signs of complete or very good partial response to antifungal therapy. Surgical resection of residual nodules or cavities should be performed whenever possible, and secondary antifungal prophylaxis with the clinically effective antifungal agent should be used before, during and after period(s) of neutropenia, although their are no studies to definitely support their use.

On the other hand, patients with active or only partially responsive infections have a high risk of developing a progressive fungal infection, and these subjects should be considered for novel treatment approaches such as high-doses of lipid formulations of AmB, granulocyte transfusions during the period of aplasia[23,34] and/or the use of novel cytokines which stimulate the antifungal properties of neutrophils and/or monocytes/macrophages, such as γ-interferon, alone or in combination with G-CSF.[35,36] Otherwise, patients with an active IFI should not proceed to an elective procedure such BMT, PBSCT or consolidation CHT for an acute leukemia[37] unless the infection is clearly responding to standard medical therapy.[38]

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