Persistent poor long-term prognosis of allogeneic hematopoietic stem cell transplant recipients surviving invasive aspergillosis

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ABSTRACT

Background
Voriconazole treatment increases early survival of allogeneic hematopoietic stem cell transplant recipients with invasive aspergillosis. We investigated whether this survival advantage translates into an increased long-term survival.

Design and Methods
This retrospective study involved all patients with an invasive aspergillosis diagnosis transplanted between September 1997 and December 2008, at the Saint-Louis Hospital, Paris, France. The primary end point was survival up to 36 months. Survival analysis before and after 12 weeks, as well as cumulative incidence analysis in a competing risk framework, were used to assess the effect of voriconazole treatment and other factors on mortality.

Results
Among 87 patients, 42 received first-line voriconazole and 45 received another antifungal agent. Median survival time was 2.6 months and survival rate at 36 months was 18%. Overall, there was a significant difference in the survival rates of the two groups. Specifically, there was a dramatic difference in survival rates up to ten months post-aspergillosis diagnosis but no significant difference after this time. Over the first 36 months as a whole, no significant difference in survival rate was observed between the two groups. First-line voriconazole significantly reduced aspergillosis-attributable mortality. However, first-line voriconazole patients experienced a significantly higher probability of death from a non-aspergillosis-attributable cause.

Conclusions
Although the prognosis for invasive aspergillosis after stem cell transplantation has dramatically improved with the use of voriconazole, this major advance in care does not translate into increased long-term survival for these severely immunocompromised patients.

Key words: invasive aspergillosis, hematopoietic stem cell transplantation, voriconazole, survival, infection.

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Introduction

Invasive aspergillosis (IA) is a common cause of infection-related mortality in hematopoietic stem cell transplant (HSCT) recipients although several large studies have demonstrated that post-transplant IA outcomes in HSCT patients have significantly improved over the last decade. This improvement in response rate and survival is attributed to the availability of better antifungal agents (i.e. agents that are more effective and better tolerated). In addition, although it is more difficult to demonstrate, the improvement is also attributed to earlier diagnoses of infection due to increased awareness on the part of the physician and the availability of effective diagnostic tools, such as galactomannan (GM) testing and CT scanning.[1-5] Voriconazole treatment appears to be independently associated with improved survival through a decrease in IA-attributable mortality.[1,2,4,6,7] These findings support other available evidence in legitimizing the universal recommendation of voriconazole as a first-line IA treatment in hematologic and other immunocompromised patients.[8-11]

Most studies have examined 3-, 4- or 6-month survival rates of HSCT recipients with IA, but immunosuppression is a persistent problem in this patient population. We, therefore, examined whether the early survival advantage could translate into an increase in long-term overall survival in our series of HSCT recipients with IA.

Design and Methods

We retrospectively studied all consecutive patients receiving an allogeneic HSCT between September 1997 and December 2008, and who were given a diagnosis of proven, probable or possible IA. Patients who had a history of IA prior to the transplant date were excluded. The study was approved by the ethics' committee of the Saint-Louis Teaching Hospital in Paris, France.

Definitions

EORTC/MSG 2008 definitions were used to define proven, probable or possible IA.[12] It should be noted that patients with possible IA were included in the study if an alternative diagnosis had been ruled out. Patients with acute myeloid leukemia and acute lymphoid leukemia in first complete remission, patients with chronic myelogenous leukemia in first chronic phase, and patients with non-malignant diseases were considered to be standard-risk patients, as opposed to poor-risk patients. Causes of death were defined as follows: for death without aspergillosis, the death had to be clearly attributed to a cause other than IA. The subject had to have no evidence of IA upon autopsy (when available) or had to have a complete IA response (CR) at the last assessment prior to death. For death with aspergillosis, the death had to be clearly attributed to a cause other than IA, even though at the time of death or last assessment there was evidence of IA. Any death occurring in cases of stable/progression of aspergillosis was assessed as from aspergillosis. The GM antigen was detected in the serum using a sandwich immunocapture ELISA (Platelia Aspergillus, Bio-Rad, Marne la Coquette, France) with a rat anti-GM monoclonal antibody, EB-A2, which recognizes the (1→5) β-D-galactofuranoside side chain of the GM molecule and can thus function as a capturing and detecting antibody. The procedure was carried out according to the manufacturer's instructions. Positive and negative controls were included in each assay. The results were expressed as an index of positivity, and the results were considered positive if the index value was 0.5 or over. The assay was performed at our hospital from 1996 onwards and its use was dictated by routine screening needs and/or suspicion of fungal disease. As first-line therapy for IA before voriconazole became available, most patients received liposomal amphotericin B. By 2002, voriconazole had largely replaced the use of any amphotericin B product, and caspofungin was sometimes used, mainly in addition to voriconazole. The responses to antifungal treatment were assessed as recently recommended,[13] and a data review committee assessed the responses in each case (GS1, PR and AB).

Statistical analysis

All data are reported as count (percent), median (range). Date of IA diagnosis was considered as start of study for each subject. The overall survival curves were estimated using a Kaplan-Meier product-limit estimator and compared using log rank or Gehan-Wilcoxon tests, according to whether the proportional hazards could be assumed or not. The factors associated with survival were analyzed using Cox's proportional hazards models. Separate models were estimated for survival up to 12 weeks and for survival between 12 weeks and 36 months in patients surviving at least 12 weeks. The proportional hazards assumption was checked by examining the Schoenfeld residuals and a Grambsch and Therneau's lack-of-fit test.[14] The following factors were analyzed: receipt of first-line voriconazole, age, disease risk, donor type, stem cell source, myeloablative *versus* reduced intensity conditioning, patient CMV status, active graft-*versus*-host-disease (GVHD) at IA diagnosis, neutrophil count and cumulated dose of steroids in the week preceding the IA diagnosis, and sites of pulmonary infection (unilateral *vs*. bilateral). For survival after 12 weeks, CR prior to 12 weeks was also considered. All deaths from IA, with IA or without IA were analyzed in a competing risk framework. Cumulative incidence curves were estimated using a standard methodology.[15] The cumulative incidence curves were compared using Gray's tests.[16] The cumulative incidence of partial responses (PR) and CR was also estimated in a competing risk framework, with death being the competing event. To further analyze the relationship between CR and survival, multistate models were used, and CR was also considered as a time-dependent variable in the proportional hazards models. All tests were two-tailed and $P<0.05$ was considered significant. All analyses were performed using the statistical software R version 2.10.1 (R Development Core Team, 2009, Vienna, Austria). The multistate models were fitted using the mstate package.[17]

Results

Between September 1997 and December 2008, 1,120 allogeneic HSCTs were performed at our center. Of these patients, 89 were given a diagnosis of possible (n=9), probable (n=67) or proven (n=13) IA. Two patients did not receive any antifungal treatment and were excluded from subsequent analyses. Of the 87 patients who received antifungal treatment, 42 (the voriconazole group) received first-line voriconazole (n=4 together with caspofungin), and 45 (the non-voriconazole group) primarily received a lipid formulation of amphotericin B (n=25), amphotericin B deoxycholate (n=10), caspofungin (n=8) or itraconazole (n=2). It is important to note that 16 patients received voriconazole as a second-line treatment; this was initiated after a median time of nine days following a non-voriconazole first-line treatment (range 1-80 days). Conversely, 18 patients in the voriconazole group received another antifungal as a second-line treatment, initiated after a median time of 28 days (9-400 days). Voriconazole

was stopped because of intolerance (n=10), insufficient efficacy (n=5), concomitant mucormycosis diagnosis (n=2). In one case the reason was not specified. Second-line antifungals were caspofungin (n=6), posaconazole (n=6), liposomal amphotericin B (n=5), and itraconazole (n=1). Voriconazole was later resumed in 10 patients.

The characteristics of the patients with IA and their causes of death, according to voriconazole as first-line treatment, are shown in Table 1.

Survival

Median follow up was 70 months (range 11-130 months): 44 months in the voriconazole group and 88 months in the non-voriconazole group. Median survival was 2.6 months and overall survival at 36 months was 18% (95% CI: 11-28%) (Figure 1A). Overall, there was a significant difference in the survival rates of the two groups (P=0.020) with a median survival time of 3.3 months in the voriconazole group and 1.5 months in the non-voriconazole group. However, while the differences in survival were quite dramatic up to ten months, the two survival curves became very closely aligned after one year. At 12 months, the survival rate was 26% (95% CI: 15-43%) in the voriconazole group and 20% (95% CI: 11-36%) in the non-voriconazole group. At 18 months, the percentages of surviving patients were identical in both groups: 20% (95% CI: 11-36%) in patients who did not receive voriconazole as first-line treatment and 21% (95% CI: 11-38%) in patients who did receive voriconazole (Figure 1B). The effect of voriconazole as a first-line treatment on mortality was not constant over time (P=0.002, Grambsch and Therneau's test). After adjusting for age, stem cell source donor type, conditioning, active GVHD at diagnosis of IA, and cumulated dose of steroids in the week preceding diagnosis of IA, first-line treatment with voriconazole was found to decrease mortality during the first 12 weeks by approximately 70% (HR=0.31, 95% CI: 0.16-0.60; P=0.0005) (Table 2). An analysis of long-term mortality risk factors (< 36 months) for survivors at 12 weeks failed to identify any significant predictor of mortality (Table 3). Over the first 36 months, no significant gain in survival was observed in the voriconazole group compared with the non-voriconazole group (mean difference 1.3 months, 95% CI: -4.2 to 6.9). The type of IA diagnosis (definite/probable/possible) had no influence on 12-week (P=0.13) or long-term survival (P=0.61).

Prognostic impact of achieving complete response of invasive aspergillosis

Eighty-six patients were evaluated for IA response to treatment. The cumulative probability of CR and PR at 12 weeks was estimated at 20% in the non-voriconazole group and 38% in the voriconazole group (P=0.074). In total, 30 patients achieved CR, 11 in the non-voriconazole group and 19 in the voriconazole group. The overall probability of CR was 25% and 45% in each group, respectively (P=0.068). The median time to CR was 3 months (range 1-6) in the non-voriconazole group and 2 months (range 0.5-24) in the voriconazole group. While all CR cases were observed during the first six months in the non-voriconazole group, 6 out of the 19 CR cases in the voriconazole group occurred between 6 and 24 months. The probabilities shown in Figures 2A and B illustrate that although a higher rate of CR was obtained in the voriconazole group, the overall mortality rate became similar in both groups

Table 1. Patients' characteristics and causes of death according to receipt of voriconazole as first-line treatment.

	No voriconazole (n=45)	Voriconazole (n=42)
Median age, years (range)	40 (5-57)	33 (7-31)
Male gender (%)	24 (53)	28 (67)
Underlying disease (%)		
Acute myeloid leukemia	3 (11)	11 (26)
Myelodysplasia	4 (9)	6 (14)
Acute lymphoid leukemia	11 (24)	5 (12)
Non-Hodgkin's lymphoma	5 (11)	8 (19)
Aplastic anemia	8 (18)	8 (19)
Other	3 (2)	2 (5)
Standard risk transplant (%)	21 (48)	18 (43)
Stem cell source (%)		
Bone marrow	29 (64)	21 (50)
Peripheral blood stem cells	10 (22)	15 (36)
Cord blood	6 (13)	6 (14)
Donor type (%)		
Genoidentical sibling	23 (51)	9 (21)
Mismatched related	1(2)	1 (2)
Matched unrelated	12 (27)	18 (43)
Mismatched unrelated	9 (20)	14 (33)
Recipient CMV positive (%)	25 (60)	25 (61)
Myeloablative conditioning (%)	35 (81)	25 (60)
Total body irradiation 12Gy (%)	18 (40)	12 (29)
Active graft-*versus*-host disease at IA diagnosis (%)	25 (56)	18 (43)
Acute	16 (36)	19 (45)
Chronic	4 (9	5 (12)
Mechanical ventilation/hemodialysis	0	0
Granulocytes/mm^3, median (range) x10^9/mm^3	1000 (0-12000)	1805 (100-7000)
Corticosteroid dose (mg/kg) at IA diagnosis (mg/kg), median (range)	1 (0-7)	1 (0-4)
Cumulated corticosteroid dose over previous 7 days, median (range)	7 (0-48)	8 (0-32)
Years of IA diagnosis (%)		
Up to 2002	32 (71)	5 (12)
From 2003	13 (29)	37 (88)
Serum galactomannan antigen positive/tested (%)	34/42 (81)	30/42 (71)
Type of IA diagnosis (%)		
Proven	8 (18)	5 (12)
Probable	32 (71)	33 (79)
Possible	5 (11)	4 (10)
Time interval between transplant and IA, days, median (range)	108 (6-974)	109 (5-1105)
IA onset within 30 days from transplant (%)	9 (20)	6 (14)
Bilateral pulmonary lesions (%)	27 (71)	16 (46)
Achieved IA complete remission (%)	11 (25)	19 (45)
Achieved IA complete remission before 12 weeks (%)	5 (11)	10 (24)
Number of deaths (%)	36 (80)	35 (83%)
12-week survival (95%CI)	36 (24-53)	60 (46-76)
12-month survival (95%CI)	20 (11-36)	26 (15-43)
Causes of death (%)		
Deaths from IA and with IA*	34 (76)	25 (60)
From IA	21 (47)	8 (19)
With IA	13 (29)	17 (40)

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Death without IA	2 (4)	10 (24)
Fungal infection (not IA)	0	2 (5)**
Infection (not fungal)	1 (2)	2 (5)
Graft-*versus*-host disease	0	2 (5)
Relapse	1 (2)	3 (7)
Idiopathic pneumonia syndrome	0	1 (2)

*For death with aspergillosis, the death had to be clearly attributed to a cause other than IA, even though at the time of death or last assessment there was evidence of IA. Any death occurring in cases of stable/progression of aspergillosis was assessed as from aspergillosis. **Fungal infections were one invasive candidiasis and one Pneumocystis jirovecii pneumonia. IA: invasive aspergillosis.

after 12 to 18 months, with a lower probability of death without CR but a higher probability of death after CR. At 36 months, the probability of being alive after CR was 18.2% in the non-voriconazole group and 15.3% in the voriconazole group (P=0.72). Using multistate models, the time to achieve CR was not found to be significantly associated with survival (P=0.47).

Causes of death

The cumulative incidence of deaths from the various causes is shown in Figure 2C and D. Patients who did not receive voriconazole as a first-line treatment had a higher probability of dying from IA than those who did (P=0.004), with an 18-month cumulative incidence of deaths from IA of 47% (95% CI: 31-61%) in the non-voriconazole group as compared to 19% (95% CI: 9-33%) in the voriconazole group (Figure 2C). The 18-month cumulative incidence of deaths with IA was similar in both groups (29%, 95% CI: 16-43%) for the non-voriconazole group and 38% (95% CI: 23-56%) for the voriconazole group, (P=0.46). The 18-month cumulative incidence of deaths without IA was 4% (95% CI: 1-14%) in the non-voriconazole group and 27% (95% CI: 14-42%) in the voriconazole group (P=0.006) (Figure 2D). Finally, the 18-month cumulative incidence of deaths from and with IA was 76% (95% CI: 60-86%) in the non-voriconazole group and 57% (95% CI: 41-70%) in the voriconazole group (P=0.021). Causes of death are listed in Table 1. Interestingly, the cumulative incidence at 12 months of deaths due to relapse of the underlying disease was 4% in the non-voriconazole group and 7% in the voriconazole group, and there was no significant difference in the cumulative incidence of relapse-related deaths over time (P=0.13).

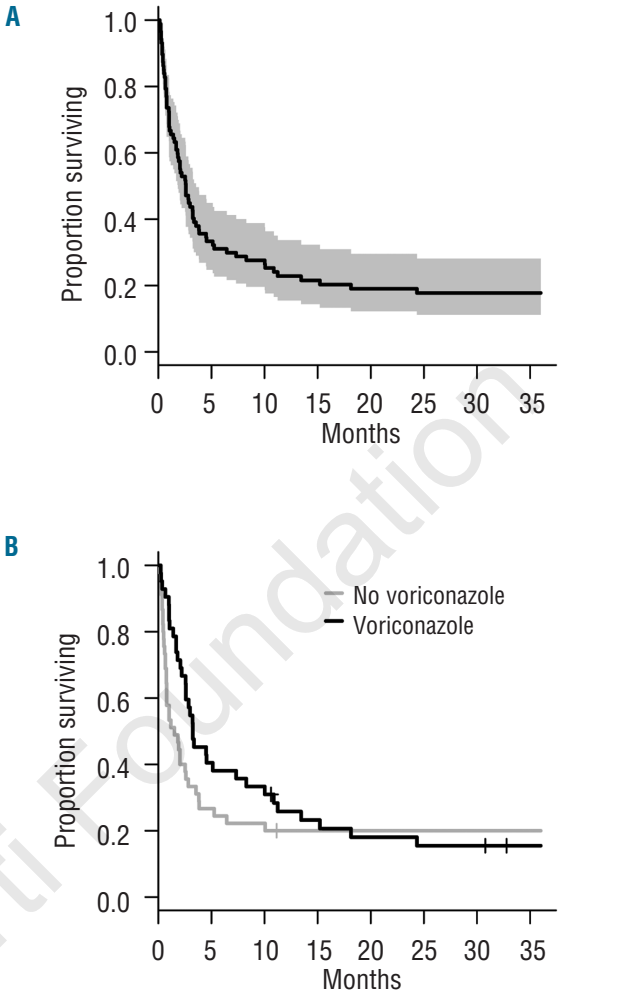

Figure 1. (A) Overall survival of 87 allogeneic transplant recipients with invasive aspergillosis. (B) Survival according to first-line treatment either without voriconazole (n=45) or with voriconazole (n=42). In (A), the shaded area represents the point wise 95% confidence interval.

Discussion

This single-center retrospective study confirms previous findings indicating that first-line voriconazole treatment of allogeneic HSCT recipients with IA leads to a significant increase in 12-week survival through a decrease in IA-attributable mortality.[2-4,6] However, an unexpected finding was that first-line treatment with voriconazole, which has mostly been prescribed during the last decade, does not translate into an increase in long-term survival.

Our study once again demonstrates the clear positive impact of first-line voriconazole treatment on 12-week survival of HSCT patients. This impact has already been demonstrated in a large randomized trial of immunocompromised patients with IA, half of whom received first-line voriconazole. In this latter study, the 12-week survival rate was 71% in the voriconazole group and 58% in the control group.[1] The difference was even larger (65% and 45%, respectively) in the subgroup of HSCT recipients (R Herbrecht, unpublished data, 2004). These figures are completely in line with our study in which the 12-week survival rate was 60% in the voriconazole group and 36% in the non-voriconazole group. Two other large retrospective and two prospective series of patients highlight the beneficial role of voriconazole on 12-week survival.[2,4,6,18] In addition, analyses of prognostic factors verify the other previously recognized important prognostic factors (uncontrolled GVHD, steroids dose).[2,4,7,19,20]

There are few reports on the long-term survival (≥ one year) of allogeneic HSCT recipients with IA. The overall one-year survival rate was 20% for Seattle IA patients receiving transplants between 1993 and 1998, while survival was only 7% for the cohort receiving transplants between 1987 and 1993.[21,22] The Seattle group also reported a one-year survival rate of 13-28% according to the

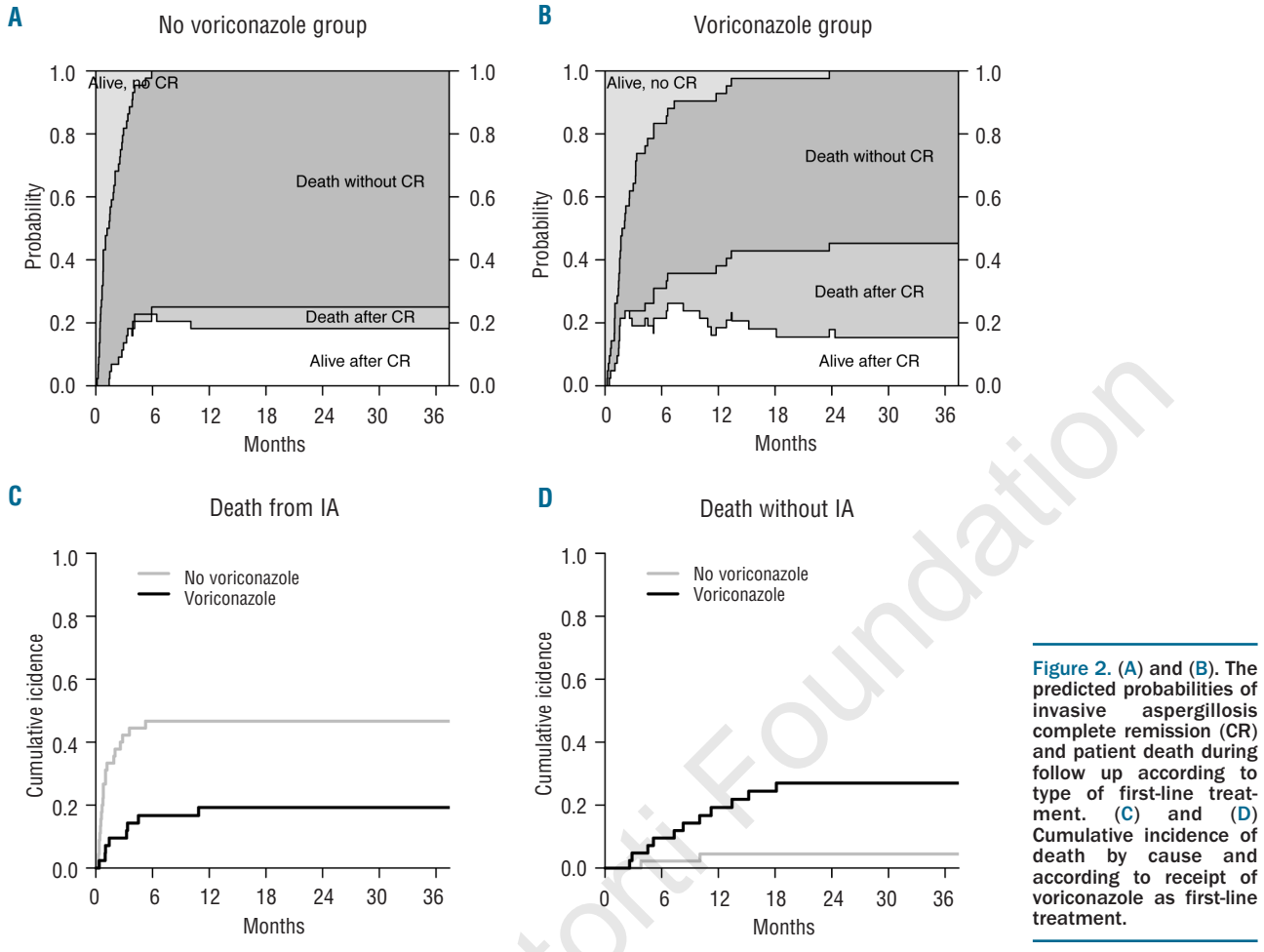

Figure 2. (A) and (B). The predicted probabilities of invasive aspergillosis complete remission (CR) and patient death during follow up according to type of first-line treatment. (C) and (D) Cumulative incidence of death by cause and according to receipt of voriconazole as first-line treatment.

year of diagnosis, with the best results being observed in the more recent patients (the 2002-2004 cohort *vs.* the 1990-2001 cohort).[2] The more recently published TRANSNET database overview, which prospectively enrolled HSCT recipients with invasive fungal infections from 23 US centers between 2001 and 2006, illustrated an overall one-year survival rate of 25.4% for 425 IA patients, including a quarter of autologous transplant recipients.[23] We have previously reported a one-year survival rate of 22% for 26 patients with IA receiving transplants in our unit in 1994.[19] The one-year survival rate of the present series, which includes none of these former 26 patients, is in line with previously published results. We could not identify any significant predictor of long-term mortality for patients living longer than 12 weeks. However, as only 25 patients died during this period, the power of these analyses was low. Interestingly, achieving a complete response to antifungal therapy is a prerequisite for long-term survival, although the time necessary to achieve this response did not seem to have any influence. Although consistent with expectations, the mandatory achievement of complete IA response for long-term survival has not been previously reported. Conversely, complete IA response alone is not enough to ensure long-term survival because of subsequent fatal complications. Voriconazole significantly decreased IA-attributable mortality, as previously demonstrated.[2,4] However, patients in the voriconazole group were unexpectedly found to experience a significantly higher mortality rate during follow up, with GHVD and other infections as the main causes of death. Although these patients recovered from IA, they remained at high risk for other complications, which overwhelmed the initial survival benefit.[24]

Our study has several limitations. Firstly, it is a retrospective study that includes patients treated more than a decade ago (1997-2008). In this respect, the two groups of patients may not be directly comparable with some factors favoring the earlier group (e.g. more genoidentical donors in this group) and others favoring the more recent one (e.g. an earlier diagnosis illustrated by a smaller number of bilateral pulmonary IA). Furthermore, it cannot be excluded that the more recent group of patients was, independently of IA, more severely ill or immunosuppressed. It may well be the case that, in the non-voriconazole period, the most vulnerable patients died rapidly from IA while less severely ill patients were long-time survivors, and that voriconazole cured most patients with IA independently of the degree of underlying illness, leaving them at risk of other complications. Techniques for causal inference in observational data, such as propensity scores or marginal structural models, may have helped to diminish biases when comparing the two groups. However, the limited sample size in the present study makes their use extremely problematic. Nevertheless, analyses adjusted

Table 2. Multivariate Cox's regression analysis of the risk factors associated with 12-week mortality.

	HR (95%CI)	P
First-line voriconazole	0.31 (0.16-0.60)	0.0005
Non-genoidentical donor	1.83 (0.94-3.54)	0.075
Active graft-*versus*-host disease	2.03 (1.02-4.45)	0.043
Cumulative dose of steroids ≥ 7 mg/kg	2.24 (1.12-4.48)	0.023
Reduced-intensity conditioning	0.96 (0.49-1.86)	0.90

Table 3. Univariate Cox's regression analysis of risk factors associated 1 with mortality between 12 weeks and 36 months.

	HR (95%CI)	P
Non-genoidentical donor	1.38 (0.59-3.20)	0.45
Reduced-intensity conditioning	1.46 (0.64-3.33)	0.36
Poor risk transplant	1.27 (0.57-2.87)	0.56
Recipient CMV positive	1.45 (0.65-3.23)	0.37
Active graft-*versus*-host disease at IA diagnosis	1.79 (0.81-3.92)	0.15
Cumulative dose of steroids ≥ 7 mg/kg	1.63 (0.74-3.58)	0.22
Voriconazole as first-line treatment	1.88 (0.78-4.51)	0.16
Achieved IA complete remission before 12 weeks	0.88 (0.39-2.00)	0.74

IA: invasive aspergillosis.

for prognostic factors, which are a way to correct for group imbalances, also confirmed raw analyses. The occurrence of invasive aspergillosis in allogeneic HSCT recipients should, therefore, be considered a strong marker of severe long-lasting immunosuppression and accompanying fatal complications.

The second limitation is that, during the study period, there was no homogeneous protocol for antifungal treatment response assessment. In most cases, clinical and imaging follow up was the sole responsibility of the consulting physician, which renders the data concerning response times to antifungal treatment somewhat imprecise. However, response times did not seem to affect the outcome.

A third limitation is that very few autopsies were performed in this study, weakening the cause-of-death data. However, each patient chart was reviewed by two of the authors (GS and PR), and the same definitions were used for both groups of patients.

Finally, the present series only includes a small number of patients. However, the study was carried out in one single transplant department and most results were obtained with such a high confidence level that it is unlikely that they could have been observed by chance alone.

This study clearly demonstrates that although the prognosis of IA after HSCT has dramatically improved with the preferential use of voriconazole as a first-line treatment, this major advance in patient care does not translate into increased long-term survival. With these patients, careful and prolonged attention must be focused on GVHD treatment as well as infection prophylaxis and detection, and curative treatment.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

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