Invasive aspergillosis remains the primary cause of death from infection following allogeneic stem cell transplantation. Most cases occur during the second or third month after transplantation, during graft-versus-host disease or immunosuppression. Strategies for management of these cases include the development of more effective antifungals for prophylaxis, the use of biological markers to improve the early diagnosis of aspergillosis, new approaches to transplantation to reduce the risk of infection, and the emerging area of targeted cellular therapy.

**Keywords** aspergillosis, allogeneic stem cell transplantation

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**Introduction**

Despite considerable progress in the management of infectious complications, invasive aspergillosis (IA) infection remains the primary cause of infectious death after allogeneic stem cell transplantation (SCT). The one-year survival rate after *Aspergillus* infection in allogeneic SCT is about 20% [1], and SCT patients always have the highest case-fatality rate among patients with *Aspergillus* infections [2] as well as the highest risk of treatment failure. It is usually difficult to separate deaths due to IA from those associated with the underlying disease or other SCT complications. However, the occurrence of IA undoubtedly has a major impact on the life expectancy of these patients, and the transplant community must focus on an approach to reduce its incidence following SCT.

**Epidemiology, outcome, and risk factors**

Owing to the development of autologous transplantation with peripheral stem cells, neutropenia in this setting lasts now less than 10–12 days, and consequently the risk of IA is almost negligible, except in patients with poor quality graft. The allogeneic SCT population remains the population with the higher risk, regardless of the type of transplant or donor-recipient HLA disparity. After allogeneic SCT, reported IA incidence varies from 0%–20%, with a higher incidence in older patients and those receiving unrelated or mismatched grafts [1]. Most cases are now observed after recovery from neutropenia, during the second or third month post-SCT, at the time of acute graft-versus-host disease (GVHD) or immunosuppression due to high dose steroids or other immunosuppressive drugs.

The one-year cumulative incidence of aspergillosis was shown to have increased from 1992 to 1998 at the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle, WA, USA. [1]. Multiple etiologies may be hypothesized to explain this increase:

1. Better survival from the early complications of transplantation
2. Changes in the transplant approach, such the increasing use of cord blood (which is associated with prolonged neutropenia) or peripheral stem cell transplants (which provide a higher risk of GVHD than bone marrow transplantation)
3. Changes in the approach to treating cytomegalovirus, with a larger use of prophylactic ganciclovir with a consequent higher risk of neutropenia.

In clinical studies, the main risk factors for IA after allogeneic SCT are: age >40 years; underlying diseases other than chronic myeloid leukemia in chronic phase or hematologic malignancy in first remission; and graft from an unrelated or HLA-mismatched donor [1]. However, even if this is difficult to analyze in clinical studies, SCT recipients have cumulative risk factors that
have been shown to be related to the risk of *Aspergillus* infection in immunocompromised hosts: neutropenia, rupture of anatomical barriers, defects in respiratory epithelial cells, monocytic and macrophage functional deficiencies, and – more recently – deficient Th-1 response to *Aspergillus* [3].

Additionally, new immunosuppressive therapies may further increase the risk from GVHD. Infliximab, a humanized monoclonal anti-TNF-alpha antibody, is used to treat steroid-resistant GVHD. Although it is difficult to determine the exact role of infliximab, GVHD, or other immunosuppressive drugs in the risk of *Aspergillus* infection, the use of infliximab has been reported to be associated with an increased risk of mould, and especially of *Aspergillus*, infections in SCT recipients with severe GVHD [4,5]. The use of any new immunosuppressive drug may provide an increase in the risk of *Aspergillus*, and its effect on the occurrence of such an infectious complication should be studied prospectively.

Another issue specific to SCT patients when compared to other immunocompromised hosts is their history. These patients have often previously undergone several neutropenic chemotherapy-induced phases, and have already been at risk of fungal infection. Consequently, some of them have prior or active *Aspergillus* infections when referred for transplant. Previous retrospective studies have shown that recurrence of *Aspergillus* following SCT occurs in roughly one-third of patients with a previous *Aspergillus* infection, especially during the early neutropenic phase [6]. A more recent study from the FHCRC shows a similar rate of post-SCT IA in pre-infected patients [7]. Additionally, it shows that the risk of recurrence of IA in such cases is higher when patients have received less than one month of antifungal therapy, and when resolution of radiographic abnormalities has not been achieved before SCT. Aside from this, the probability of overall survival is not significantly different from patients without prior IA [7]. To date, secondary prophylaxis has been recommended for these patients, but the optimal choice is unknown due to the lack of prospective studies in this setting [8].

How can the incidence of aspergillosis after SCT be reduced?

**Antifungal drugs**

Based on the results of large comparative studies carried out in the 1990s, fluconazole has been the gold standard for prophylaxis of invasive fungal infections after allogeneic SCT. However, owing to the increasing incidence of IA [1], and to the lack of activity of fluconazole against *Aspergillus*, this strategy is now the subject of debate. One of the main problems in antifungal prophylaxis is that the antifungal must reduce the risk of fungal infection, but must also take into account the complex situation of these patients, especially the risk of drug interaction, so that the benefit of antifungal prophylaxis is not outweighed by excessive antifungal-related toxicities.

Itraconazole has been shown to have a better prophylactic effect than fluconazole on the occurrence of invasive fungal infection after allogeneic SCT, but without a significant impact on survival [9,10]. Itraconazole interacts with many drugs, including cyclophosphamide and vinca alkaloids, and its use during the conditioning regimen has been associated with increased early liver toxicity [9]. Consequently, its administration should be avoided during the conditioning regimen. Owing to the therapeutic efficacy of newer antifungals, it may be considered that the best prophylactic option in SCT patients has not yet been found [11]. Studies with other antifungals are ongoing.

**Sensitive biological markers**

Several prospective studies have demonstrated that with sensitive biological markers such as galactomannan antigenemia or PCR it is possible to make an earlier diagnosis of *Aspergillus* infection compared to more traditional approaches [12–17]. Another potential benefit of such methods, although not illustrated so far, is the distinction between *Aspergillus* and other mould infections which may require different therapeutics, especially when culture samples do not grow for identification. While the risk of IA is higher in the transplant setting than in other hematologic diseases, there is no evidence to suggest that the sensitivity or specificity of these tests for the diagnosis of *Aspergillus* infection are different after SCT than in more usual situations.

**New transplant approaches**

While one of the main goals of peripheral blood SCT was to reduce the early neutropenic phase when compared to bone marrow transplantation, there is no evidence that this approach has dramatically reduced the incidence of severe infectious complications, particularly fungal infections. The main reason is probably that the early period of risk for IA is not as important as the late period, i.e., after one month, while the patient is no longer neutropenic but may suffer from GVHD and may receive steroids and/or other immunosuppressive drugs. One of the key questions
for the transplant community is now whether non-myeloablative, reduced intensity conditioning (RIC) regimens reduce the risk of fungal infection, and especially of aspergillosis. RIC regimens have the chief advantage that they considerably reduce the duration and depth of neutropenia at the early phase of transplant. Since the main period of risk for recurrence of Aspergillus infection in patients with prior IA is the early phase of transplant, the RIC approach has been used in this setting to avoid recurrence of IA. However, until now, RICs – with any conditioning regimen – seem to provide a similar risk of GVHD as do conventional approaches. Therefore, it remains hypothetical that in standard patients, the risk of Aspergillus infection may be reduced by RIC. Only historical comparisons between the classical, myeloablative approach and RIC have been published to date [18–22], these report one-year incidences of IA between 8% and 14% after RIC transplants, comparable to those observed in the same centers after conventional conditioning regimens. One interesting finding is that, as for other infections, IA usually occurs later after RIC than after the conventional regimen [20,21]. This is probably due to the later occurrence of GVHD as compared to standard transplants.

Although a reduction in fungal infections is expected from RIC regimens, only prospective, comparative studies will allow us to draw conclusions about the benefit of such approaches for reducing the risk of fungal infection.

Targeted cellular therapy

It has been shown in animal models that pulmonary dendritic cells play a major role in A. fumigatus surveillance [23] and that antigens of Aspergillus may induce both Th1- and Th2-type reactivity during infection [24,25]. These studies offer new insights into the reconstitution of the immune system after allogeneic SCT, and especially from donor cells that could be used either for prophylactic or therapeutic targeted approaches.

References

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