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Complications of hematopoietic stem transplantation: Fungal infections

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Abstract
Patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) are at increased risk of invasive fungal infections, especially during the early neutropenic phase and severe graft-versus-host disease. Mold-active prophylaxis should be limited to the highest risk groups. Empiric antifungal therapy for HSCT with persistent febrile neutropenia is associated with unacceptable response rates, unnecessary antifungal therapy, increased risk of toxicity, and inflated costs. Empiric therapy should not be a substitute for detailed work up to identify the cause of fever in such patients. The improved diagnostic performance of serum biomarkers such as galactomannan and β-D-glucan, as well as polymerase chain reaction assays has allowed the development of diagnostic-driven antifungal therapy strategies for high risk patients. Diagnostic-driven approaches have resulted in reduced unnecessary antifungal exposure, improved diagnosis of invasive fungal disease, and reduced costs without increased risk of mortality. The appropriateness of diagnostic-driven antifungal strategy for individual HSCT centers depends on the availability and turnaround times for diagnostics, multidisciplinary expertise, and the local epidemiology of invasive fungal infections. Echinocandins are the treatment of choice for invasive candidiasis in most HSCT recipients. Fluconazole may be used for the treatment of invasive candidiasis in hemodynamically stable patients with no prior azole exposure. The primary treatment of choice for invasive aspergillosis is voriconazole. Alternatives include isavuconazole and lipid formulations of amphotericin. Currently available evidence does not support routine primary combination antifungal therapy for invasive aspergillosis. However, combination salvage antifungal therapy may be considered in selected patients. Therapeutic drug monitoring is recommended for the majority of HSCT recipients on itraconazole, posaconazole, or voriconazole.

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Introduction

Fungal infections are an important complication of hematopoietic stem cell transplantation (HSCT) [1]. During the pre-engraftment phase, neutropenia, mucositis, and the presence of central venous lines increase the risk of *Candida* infections, whereas chronic graft-versus-host disease (GVHD) is associated with an increased risk of invasive mold infections, in particular aspergillosis [2,3]. Mismatched/unrelated grafts, cord blood stem cells, intensive conditioning regimens, and GVHD are all associated with prolonged neutropenia and/or delayed immune reconstitution, and hence substantially increased risk of invasive fungal infections [2,4].

The overall incidence of invasive fungal disease is approximately 8% in unrelated or mismatched allogeneic HSCT, 6% in matched related allogeneic HSCT, and less than 2% in autologous HSCT [5,6]. Invasive fungal infections are associated with considerable morbidity, high mortality rates, and increased healthcare costs [7,8]. Prevention and early recognition and treatment are therefore very important.

Antifungal prophylaxis in HSCT

Compared with fluconazole, mold-active prophylaxis in HSCT is associated with lower incidence of invasive fungal disease and decreased fungus-related mortality, but with increased toxicity-related discontinuations and no significant reduction in overall mortality [9]. Thus, expected benefits of routine antifungal prophylaxis in HSCT need to be balanced against the potential adverse effects, drug–drug interactions, and costs [10]. Autologous HSCT is associated with a low risk of invasive fungal disease and hence antifungal prophylaxis is generally not recommended [11–14]. However, fluconazole may be considered for autologous HSCT recipients at risk of severe mucositis [13]. By contrast, mold-active prophylaxis is recommended during the high risk periods of early postallogeneic HSCT neutropenia and severe GVHD requiring high dose steroids [11–13].

Randomized clinical trials of various sizes and designs have reported the results of prophylaxis in allogeneic HSCT using fluconazole, itraconazole, voriconazole, micafungin, intravenous amphotericin, and inhaled liposomal amphotericin [15–21]. Posaconazole prophylaxis in HSCT neutropenia is only reported in a small retrospective study [22]. Data are also available in the context of severe GVHD for posaconazole and voriconazole [12,23,24].

Based on the quality of the available evidence, current international guidelines recommend fluconazole or voriconazole as preferred prophylaxis agents during early allogeneic-HSCT neutropenia, and itraconazole, micafungin, or aerosolized liposomal amphotericin with oral fluconazole as alternatives [11–13]. Posaconazole and voriconazole are the preferred primary antifungal prophylaxis options for HSCT with severe GVHD; itraconazole and intravenous liposomal amphotericin are alternative choices [11–13,25].

Empiric antifungal therapy in HSCT

Empiric antifungal therapy (EAT), also known as fever-driven antifungal therapy, typically refers to the practice of starting systemic antifungal therapy in patients with persistent febrile neutropenia despite the receipt of broad-spectrum antibacterial therapy for a period of 4–7 days, in the absence of clinical or mycological evidence of invasive fungal disease [26]. This strategy was developed three decades ago in the face of growing concern over the limited diagnostic utility of the available tools leading to delayed antifungal therapy for unrecognized invasive fungal disease in high risk patients [27,28]. EAT was established as standard of care and a series of randomized clinical trials investigated the efficacy and safety of various antifungal agents against active comparators.

Two randomized trials compared fluconazole with amphotericin B deoxycholate in patients with persistent febrile neutropenia. Despite fluconazole's lack of antimold activity, there was no significant difference in overall response or breakthrough fungal infections, with significantly higher rates of toxicity and discontinuation with amphotericin [29,30]. Multiple randomized clinical trials utilized a noninferiority composite endpoint (successful treatment of any baseline fungal infection, absence of any breakthrough fungal infection, survival for 7 days or more after the completion of therapy, no premature discontinuation of study therapy and resolution of fever during neutropenia) to investigate EAT using liposomal amphotericin, voriconazole, or caspofungin. Overall response was achieved in 26.0–50.1% and defervescence in 32.5–58.1% [31–33]. In addition to the disappointingly low response rates associated with EAT, excessive numbers of patients receive unnecessary systemic antifungal therapy with consequent toxicities and added financial burden [34,35]. Furthermore, EAT may miss invasive fungal disease in patients with neutropenia or high dose corticosteroids in whom fever may be absent [36,37]. EAT without a definitive diagnosis can also result in considerable clinical uncertainty, including over the appropriate duration of EAT and the need for future secondary prophylaxis. Accordingly, EAT should not be a substitute for a thorough diagnostic work-up to identify the cause of fever and direct appropriate therapy [38].

Diagnostic-driven antifungal therapy in HSCT

There has been considerable progress over the past two decades in diagnostic tests for the diagnosis of invasive fungal diseases, including computed tomography (CT), biomarkers (e.g., galactomannan and β-D-glucan) and polymerase chain reaction (PCR) assays [39,40]. The emerging understanding of how best to utilize biomarkers in the diagnosis of invasive fungal disease has allowed the development of consensus guidelines and optimized diagnostic pathways [41,42]. The use of serum or bronchoalveolar biomarkers to guide timing of antifungal therapy in high risk patients is known as diagnostic-driven antifungal therapy (DAT) [26,38].

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