INFECTIONS IN HEMATOLOGICAL MALIGNANCIES

Management of invasive fungal infections in neutropenic patients

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The risk of infection in hematological disorders is high and changes according to the underlying disease or the type of treatment [1]. Fungal infections is a challenging field for physicians dealing with hematological patients because the underlying disease itself causes a substantial increase in the risk of infections, and the presentation and the course of infections, can be puzzling. This brings out the importance of experience and evidence in this area. Classically, fungal infections can be defined as infections occurring in patients with prolonged neutropenia but special procedures such as stem cell transplantation (SCT) can change this. The changing pattern of transplant approaches such as nonmyeloablative (NMA) transplantation, new drugs, and new indications caused some major changes in the timing of fungal infections [2–4]. The risk of having a fungal infection is around 5–8% in acute leukemias and 7–20% in allogeneic stem cell transplant recipients. The risk in autologous transplants is similar to acute leukemia patients. Although the numbers represent a small proportion of infections in SCT patients, there are a lot of problems facing the physician; the mortality of fungal infections in SCT is very high (over 80%) in SCT patients, the fungal infection is sometimes very difficult to diagnose, very difficult and expensive to treat, and prolongs the hospital stay [5–7].

Changing pattern of invasive fungal infections

There are two major changes in the pattern of invasive fungal infections in cancer patients:

1. The incidence of invasive Candida (IC) infections is reduced in the last ten years after the utilization of azole prophylaxis. While the rate of IC in SCT was around 20% in allogeneic SCT patients not receiving prophylaxis, this rate remained below 5% after the introduction of azole prophylaxis. This also reflected itself in the mortality rates, before prophylaxis, the mortality of IC in SCT was 40–50%, which decreased to 20% after azole prophylaxis. Azole prophylaxis also changed the distribution of Candida species infecting the SCT patient. While C. albicans and tropicalis are decreasing, there is an increase in non-albicans Candida infections. Aspergillus is now the dominating fungal pathogen in SCT patient with a very high mortality rate. The use of new antifungals also brings out the possibility of breakthrough infections by pathogens resistant to these new agents. Recently breakthrough Zygomycosis after Voriconazole treatment were reported [8,9].

2. New transplant approaches caused a time-shift in the occurrence of fungal infections. The initial studies performed in NMA transplants showed that there was a decrease in the rate of early Aspergillus infections in NMA patients [3]. When these patients were followed for longer periods, it was observed that approaches such as NMA transplants and donor lymphocyte infusions delay the occurrence Graft versus Host disease (GVHD) and also delays the occurrence of Aspergillus infections. Although the cumulative rate of Aspergillus infections does not decrease, there is a slight decrease in Aspergillus related mortality [3,4]. Not only the type of transplant, but also the development of GVHD, corticosteroids, T-cell depleted grafts, advanced age and CMV infection are risk factors for Aspergillus infections. Although the cumulative rate of Aspergillus infections does not decrease, there is a slight decrease in Aspergillus related mortality [3,4]. Not only the type of transplant, but also the development of GVHD, corticosteroids, T-cell depleted grafts, advanced age and CMV infection are risk factors for Aspergillus infections. The increase of invasive fungal infections in SCT patients who had received the anti-tumor necrosis factor-alpha antibody-Infliximab demonstrates the importance of non-myeloid immunity in SCT patients. As the rate of Candida infections are low in SCT
patients it is not easy to comment on the Candida infections in autologous patients [3,4].

Problems in the diagnosis of invasive fungal infections in SCT patients

Most of the SCT patients with invasive fungal infection present with fever and/or pneumonia and the differential diagnosis are not easy in this situation. Although EORTC/MSG proposed an approach based on the diagnosis of the fungal infection as possible, probable and definite, this is mainly useful in clinical trials and in evaluating the data [10]. Still, the diagnosis of fungal infection relies on non-invasive methods such as galactomannan and lately beta-glucan levels, imaging techniques such as high-resolution tomography and molecular studies [11,12].

The presence of relatively specific findings such as air-crescent sign and halo sign helps the diagnosis of fungal infection but in cases of angioinvasive aspergillosis, imaging techniques can be misleading. The initial studies on galactomannan was found to be promising with high sensitivity and specificity rates, but the following studies showed that, factors such as the determination of the cut-off levels and consecutive sampling is important in the use of Galactomannan in invasive fungal infections [11]. It is early to comment on the role of Beta-glucan test in the diagnosis of invasive fungal infections, and this test is helpful in pan fungal diagnosis [12]. The help of molecular methods are limited at this point.

Treatment options, new and old drugs

**Preemptive therapy**

When treating a cancer patient with antifungal drugs, one of the most important problems is the number of patients receiving an antifungal treatment only because of prolonged fever and neutropenia; this empiricism originates from the studies done in the 1980s. The EORTC study done in 1989 showed that adding an antifungal to the empiric treatment of neutropenic patients with fever persisting more than 4 days had a positive effect on the number of fungal infections and a marginal benefit on the number of deaths attributed to fungal infections. Although this is an accepted practice, most of the time it is not easy to feel comfortable to use such expensive and toxic agents in a patient with good clinical status but prolonged fever. To start preemptive antifungal therapy when there is no clinical sign (except fever), we need a marker showing fungal infection in the body. Monitoring galactomannan levels can be a candidate to start preemptive treatment.

**Treatment of fungal infections**

**Empirical treatment:**

Conventional Ampho-B is being used as the initial empirical treatment of fungal infections in febrile neutropenic patients but commonly the adverse events related to conventional Ampho-B precludes the use of this drug and cause a shift to another antifungal drug. When conventional Ampho-B is compared with Liposomal Amphotericin-B, they have equal efficacy overall and liposomal form is superior in terms of breakthrough fungal infections and toxicity profile [13].

When liposomal Ampho-B was compared to lipid complex form at doses of 5 mg/kg; liposomal form was found to be superior in terms of overall success (42% vs. 33.3%) and drug-related fever, and discontinuation of the drug was higher in the lipid complex form [14]. In the last few years, new generation of antifungals caused a major change in the practice of empirical treatment of fungal infections. Voriconazole; a new azole is compared with liposomal Ampho-B in empirical treatment. They were found to be equally effective with fewer deaths in the Liposomal Ampho-B group, less breakthrough invasive fungal infections in Voriconazole group [15]. The main side effects of Voriconazole are visual disturbances and hallucinations; both reversible. Caspofungin, an echinocandin was also compared with liposomal amphot-B in the empirical setting. They were equally effective. Caspofungin group experienced more eradication of baseline fungal infections and less nephrotoxicity. In both trials overall success was between 30–50% [16].

**Candida:**

Treatment of Candida spp. can be separated in 3 related topics:

1. Prophylaxis
2. Treatment of azole sensitive Candida
3. Treatment of azole resistant and refractory Candida

**Prophylaxis.** Prophylaxis has shown to be effective against Candida infections in stem cell transplant patients by Fluconazole [17]. Fluconazole prophylaxis reduced Candida albicans infections but caused an increase in non-albicans Candida spp. and also azole-resistant Candida. Oral Itraconazole was also used for prophylaxis against both Candida and Aspergillus [18]. Although the results are encouraging, the erratic bioavailability and intolerance of patients to the oral forms is a major problem [18].

**Treatment of azole sensitive Candida.** Azole sensitive Candida left its place to Aspergillus after the intro-
duction of fluconazole prophylaxis [19]. Fluconazole, being safe, effective, orally available and cheap, is the main drug of choice. The main clinical presentation is acute disseminated candidiasis and esophageal candidiasis. The success of fluconazole in this group of patients is over 70%. When compared to fluconazole, Caspofungin, voriconazole, amphotericin-B, micafungin and anidulafungin both showed similar response rates, while Caspofungin is better against C. glabrata (95% vs. 67%) [20–24].

Treatment of azole resistant Candida. After fluconazole prophylaxis, azole resistant Candida spp. such as C. krusei increased. New antifungals such as posaconazole, caspofungin, micafungin and anidulafungin are effective against azole resistant and refractory Candida [20–23].

Aspergillus

Aspergillus is the main pathogen responsible for fungal infections in cancer patients and it is the first cause of infectious death after stem cell transplant [24]. The incidence of invasive aspergillosis (IA) increased in the last 10 years and the incidence is 3–8% in acute leukemia, 1% in autologous transplants and 5–25% in allogeneic transplants. The number of unrelated transplants and older patients treated are increasing and an increase in the number of Aspergillus infections seems to be unavoidable.

The mortality rates are unacceptably high, especially in stem cell patients and probability of survival remained below 25% in patients with probable and proven Aspergillosis. The diagnostic approaches are limited and there is no golden standard except showing the mould in cultures, which is nearly impossible in most of the cases [2,5]. Amphot-B is effective against Aspergillus and most of the studies performed with liposomal amphi-B showed a response rate between 55–70% in filamentous infections. Although fluconazole has no effect on Aspergillus, Itraconazole and Voriconazole are highly effective. The use of Itraconazole is limited due to bioavailability and intolerance but voriconazole is a good alternative. The comparison of Voriconazole and liposomal amphi-B in invasive aspergillosis demonstrated a good efficacy of Voriconazole (53% vs. 32%) with few side effects [25]. Caspofungin received approval from the FDA after the study performed in refractory invasive aspergillosis [26]. In this study patients with documented Aspergillosis, not responding to any other antifungal received Caspofungin and 50% responded (26/52).

Combination therapy

One of the best advantages of the new antifungals is better toleration and fewer side effects. This has prompted the use of a combination of antifungal drugs, especially in refractory patients. In a retrospective analysis, the addition of caspofungin to amphoterin to amphoterin resulted in improvement in 42% of 48 patients who had progressing proven or possible aspergillosis despite liposomal amphoterin monotherapy. The results of the preclinical data does not necessarily convert to clinical efficacy. Although there is no data that strongly supports the use of combinations in antifungal treatment, there are many limited reports that supports the use of combinations as salvage treatment. There is still a need for a large, multicentric study that will assess the role of combinations in fungal infections.

Conclusion

There has been a remarkable progress in developing new drugs in the treatment of fungal infections. The demonstration of efficacy of posaconazole, anidulafungin and miconazole in the treatment of common and rare fungal pathogens shows that there is still more to say in this area. The main problems are the lack of definite markers to diagnose and to monitor fungal infections, the high cost of antifungal treatment, the toxicity of the antifungal agents, the future of combination therapies and the high rate of mortality especially in refractory patients. New diagnostic tests, more data coming from new trails and old studies will help us to achieve better results, and save more patients.

References


