Use of liposomal amphotericin B in bone marrow transplant

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ABSTRACT
Increasing number of transplants worldwide has resulted in an increase in the incidence of fungal infections. Prolonged neutropenia, immunosuppression and graft vs. host disease all result in high predisposition to fungal infections. The likelihood of developing a fungal infection increases with the severity and duration of neutropenia, which, in the case of cancer or chemotherapy for the treatment of hematological malignancies, can range from a few days to several weeks. Invasive fungal infections are difficult to diagnose and neutropenic patients with fever often receive empirical antifungal therapy. This provides a rationale for the prophylactic use of antifungal agents. The empirical use of liposomal amphotericin B has overcome some of the difficulties usually found in this setting. The majority of clinical efficacy data related to liposomal amphotericin B are derived from compassionate use studies and case series. The major advantage of these liposomal formulations of amphotericin B is a reduction in amphotericin toxicity. Use of liposomal amphotericin has been shown to be a cost-effective approach abroad and the same has been our experience also. Commercially ambisome and Fungisome are the only products that contain true liposomes. Unlike ambisome, which needs to be used in dose of 3 mg/kg/day Fungisome™ is effective in the dose of 1–3 mg/kg bodyweight. The Indian liposomal preparation has shown to be safe and effective used in over 150 transplant patients in our experience. We conclude that the liposomal amphotericin is better-tolerated and also gives better responses in documented fungal infections.

KEY WORDS: Bone marrow transplant, fungal infections, liposomal amphotericin B

Bone marrow transplant (BMT) or haemopoietic stem cell transplant (HSCT) is being applied for a variety of conditions including leukaemia, haemoglobinopathy and aplastic anemia. More recently, BMT has also been used as a potentially curative modality in autoimmune diseases. The indications for BMT and HSCT are therefore expanding. A survey done in Europe confirms its increasing application. Gratwohl et al. indicated that the number of stem cell transplants performed in Europe has been over 132,963 in one decade.1 There are over 700 centers in Europe performing BMT/stem cell transplants. Currently almost 10,000 transplants are taking place each year. Some of the increasing applications of transplantation include reduced intensity ‘nonmyeloablative’ ‘mini’ transplants for solid tumours. Improvements in supportive care have lead to significantly decreased mortality from transplants. Fungal infections often contribute to significant mortality and morbidity associated with transplants.

Fungal infections in BMT setting
Prolonged neutropenia, use of immunosuppressive agents, presence of graft vs. host disease, and use of corticosteroids predispose transplant patients to fungal infections. Delayed engraftment, nonengraftment, graft-failure, and other such situations lead to particularly prolonged neutropenia in the BMT setting. Allotransplantation with mismatched related donor transplants, matched unrelated donor transplants (MUD transplants) often requires significant immunosuppression and is often associated with problematic fungal infections. Graft vs. host disease results in significant problems related to delayed immune function recovery as well as attendant increased immunosuppression, which further predisposes to fungal infections. Use of corticosteroids is a well-known risk factor for fungal infections and transplant recipients often receive corticosteroids for a variety of reasons, the most important being graft vs. host disease.

Invasive fungal infections
Invasive fungal infections are difficult to diagnose and neutropenic patients with fever often receive empirical antifungal therapy. More than half of the fatal infections in neutropenia patients are due to fungi with Candida, Aspergillus, and Mucormycosis the most commonly observed pathogens. The temporal profile of fungal infections in BMT is depicted in Figure 1. Candidaemia and invasive Candidiasis have become an increasing concern in hospitals around world with published reports indicating that Candida species are the fifth most common organism isolated from blood stream in BMT patients. Liposomal amphotericin B is approved for the treatment of candidaemia and candidiasis due to its superior efficacy and safety relative to conventional amphotericin B.
Invasive aspergillosis has been associated with poor outcome in allogeneic BMT recipients. In one series, only 10% were cured despite half of the patients receiving liposomal amphotericin B. Immunosuppression aggravated by GVHD and its treatment as well as dissemination of invasive aspergillosis seem to be major factors in the poor prognosis. Ozsahin et al. reported on successful treatment of invasive aspergillosis in chronic granulomatous disease using bone marrow transplantation, granulocyte colony-stimulating factor-mobilized granulocytes and liposomal amphotericin B. This report illustrates the importance of granulocytes and liposomal amphotericin B in eradicating invasive fungal infections.

Mucormycosis has been reported in patients with leukemia, lymphoma, and bone marrow transplant recipients. It carries an extremely poor prognosis. Only aggressive and early liposomal amphotericin B treatment with early neutrophil recovery seemed to help. In this regard, use of liposomal amphotericin appeared to be beneficial for a dose of 3–5 mg/kg/day for 4 weeks followed by 3 mg/kg/day till neutrophil recovery (total dose given is 12 g).

Allogeneic stem cell transplant recipients are considered to be high-risk patients susceptible to fungal infection and nephrotoxicity. Walsh et al. presented results of a comparative trial of liposomal vs. conventional amphotericin B for empirical treatment of patients with fever and neutropenia. They found that based on efficacy, liposomal amphotericin B at a dose of 3 mg/kg/day was equivalent to conventional amphotericin B 0.6 mg/kg/day as empirical therapy but was associated with significantly fewer side effects. A subset of 103 patients from the Walsh study that received allogeneic stem cell transplantation was analyzed separately (Table 1). Nephrotoxicity defined as a doubling of baseline creatinine, occurred in one-third of the patients receiving liposomal amphotericin B, but was significantly greater in the patients on conventional amphotericin B. There were five patients on conventional amphotericin B, who required hemodialysis compared to one on liposomal amphotericin B. Dose reductions were required in 60% of patients in the conventional amphotericin B group compared to 17% of patients in the liposomal amphotericin B group. They did not find any significant differences in hepatotoxicity between liposomal amphotericin B and conventional amphotericin B groups.

Use of conventional amphotericin B in the BMT setting

Conventional amphotericin B has been used as part of empirical therapy for neutropenic fever post-transplant as well as prophylaxis for invasive fungal infections. This has resulted in a wealth of clinical experience. However, its use is limited due to the associated problems.

Drawbacks of conventional amphotericin B particularly relevant to BMT

The particular drawbacks of conventional amphotericin B with respect to BMT include inability to administer total required dose, problems with renal impairment, electrolyte imbalance, and tolerability. Also conventional amphotericin B often contributes to serious problems like platelet refractoriness.

Liposomal amphotericin B in BMT

The empirical use of liposomal amphotericin B has overcome some of the difficulties usually found in conventional amphotericin B. The majority of clinical efficacy data related to liposomal amphotericin B are derived from compassionate use studies and case series. The major advantage of these liposomal formulations of amphotericin B is a reduction in amphotericin toxicity. Use of liposomal amphotericin has been shown to be a cost-effective approach abroad and the same has also been our experience.

In one of our earlier studies of 66 patients, who underwent bone marrow transplant at the Tata Memorial Hospital, the incidence of fungal infection was 25.75%. Invasive candidiasis accounted for 15.15% of these infections and the rest 10.60% were due to invasive aspergillosis. Since 2001, after initiating use of liposomal amphotericin B in selected cases, the morbidity and mortality associated with fungal infections has reduced. We have used liposomal amphotericin B in a dose of 1–3 mg/kg body weight. In Table 2 details of individual clinical situations, where liposomal amphotericin B was used with

Table 1: Nephrotoxicity in allogeneic bone marrow transplant patients receiving either liposomal amphotericin B 3 mg/kg/day or conventional amphotericin B 0.6 mg/kg/day as empirical therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Liposomal amphotericin B</th>
<th>Conventional amphotericin B</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 x baseline creatinine value</td>
<td>32%</td>
<td>66%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemodialysis required</td>
<td>1</td>
<td>5</td>
<td>0.08</td>
</tr>
<tr>
<td>Hypokalaemia (K+ &lt;3 meq/l)</td>
<td>19%</td>
<td>14%</td>
<td>0.51</td>
</tr>
<tr>
<td>Dose reductions</td>
<td>17%</td>
<td>60%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
good effect, are depicted. After the availability of the Indian liposomal amphotericin B (Fungisome®) as opposed to the international brand, it was possible to use the liposomal preparation in many more patients due to the lower cost as well as better tolerability. In our experience, the total number of patients, who benefited from the Indian liposomal amphotericin B, exceeds 150 (some of these patients are leukemias and not transplant patients). In all these patients undergoing BMT received Indian liposomal amphotericin and benefited from the same. A multicentric randomized clinical trial to evaluate the safety and efficacy of Fungisome 1 Vs 3 mg/kg/day Vs conventional amphotericin B 1 mg/kg/day is planned to substantiate the safety and effectiveness of Indian Liposomal amphotericin B in febrile neutropenic patients.

**Advantages of liposomal amphotericin in BMT patients**

Apart from better tolerability and less side-effects the biggest advantage of liposomal preparation over conventional amphotericin B is that a cumulative dose of 5 g can be achieved quickly as it is possible to give at doses of 1–3 mg/kg/day and as already alluded reduced nephrotoxicity is another important advantage.

**Liposomal amphotericin B in pediatric bone marrow transplantation**

Ringden *et al.* reported on prophylactic and therapeutic use of liposomal amphotericin B for invasive fungal infections in children undergoing organ or allogeneic bone marrow transplantation.[6] The clinical cure rate was 86% and eradication of fungi from a deep site was verified in 80%. They concluded that liposomal amphotericin B was well tolerated in transplanted children, with few acute toxic side effects.

**Combination antifungal therapy**

So far combination of antifungal agents has not been common in clinical practice. This is because of theoretical lack of synergism between the commonly available agents. Amphotericin B and fluconazole though not antagonistic have not been documented to have any synergism. Caspofungin belongs to a new class of antifungal agent with a different mechanism of action. In a study, Kontoyiannis *et al.* found that Caspofungin in combination with liposomal amphotericin B resulted in a 42% response rate in invasive aspergillosis and was generally well tolerated.[7] This combination with or without voriconazole was used for treating refractory fungal pneumonia in children with acute leukemia undergoing BMT. It was found to be well tolerated and effective.[8] A study of combined caspofungin and liposomal amphotericin B is being planned at TMH.

**Recommendations for usage of liposomal amphotericin in BMT based on pharmaco-economic analysis**

The overall pharmacoeconomic impact of liposomal amphotericin B compared to conventional amphotericin B is well documented.[9] One of the most important factors considered was the cost of nephrotoxicity. Nephrotoxicity may either be a true factor or a surrogate marker for more ill patients. In either case it was found that the cost increased by US $3781 in patients treated with conventional amphotericin B for neutropenic fever. The corresponding cost increment was US $5506 in case of bone marrow transplant patients. Thus nephrotoxicity of conventional amphotericin B adds substantially to the overall costs and morbidity thus making liposomal amphotericin B cost effective in the transplant setting. The availability of the Indian liposomal amphotericin B (Fungisome®) has further increased the cost benefit ratio in the Indian transplant setting. The acquisition cost of Fungisome is lesser than that of other marketed liposomal preparation thus an economical option for Indian physicians.

**Conclusion**

Liposomal amphotericin B is an important advance in the antifungal armamentarium. It is also cost-effective in the BMT setting. The possibility of combination antifungal therapy particularly with newer antifungals like caspofungin needs to be explored further.

**Reference**


**Table 2: TMH BMT experience with liposomal amphotericin B: clinical situations where the same was used**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Total</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidiasis *</td>
<td>10 episodes of oropharyngeal candidiasis</td>
<td>1 episode of osteomyelitis</td>
</tr>
<tr>
<td>Aspergillosis (presumed)</td>
<td>7 episodes</td>
<td>Cavities 4, fungal ball 1, halo sign 1, BAL 1</td>
</tr>
<tr>
<td>Aspergillosis (proved)</td>
<td>3 episodes</td>
<td>Sinusitis 1, Brainaspergiloma 1, aspergillemia 1</td>
</tr>
</tbody>
</table>

Range of treatment 3–6 weeks (Total dose 1.5–5 g)

*Nonalbicans (Candida species)*


