Drug Utilization Review of Conventional Amphotericin B in Febrile Neutropenic Patients Hospitalized at a Bone Marrow Transplant Center

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Abstract

Introduction: Conventional amphotericin B is one of the antifungal choices as prophylactic and empiric treatment against fungal infections in febrile neutropenic patients. However the time of initiation, dosing and monitoring of drug adverse effects must be justified to maximize the efficacy and minimize the toxicities of this antifungal agent.

Methods: We conducted a prospective observational study at Shariati teaching hospital, Hematology – Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences to evaluate the appropriateness of amphotericin B utilization for our adult bone marrow transplant (BMT) patients for a period of six months.

Results: The charts of a total of 54 patients in 3 adult BMT wards were prospectively evaluated. Most patients underwent allogienic transplantation (61.1%). The mean duration of treatment with amphotericin was 9.3 days with 50% as prophylactic and 42.6% as empiric treatments. Appropriate dose was initiated in 70.4% of patients versus 22.2% unjustified initial doses. The use of amphotericin was appropriate in 92.6% of cases versus 7.4% unjustified uses.

Conclusion: Based on the results of this study, in the majority of our BMT patients amphotericin B was utilized appropriately either as prophylactic or empiric treatment. More attention in dose adjustment seems to be necessary to minimize nephrotoxicity and other adverse effects of this agent.

Key words: Amphotericin B, Febrile Neutropenic, Empiric and Prophylactic Treatment

Introduction

In neutropenic patients, fever can be the only sign of infection however it is not specific symptom.(1) About 60% of febrile neutropenic patients have an established or occult infection and when neurophil counts goes under 100 cells/mm3, about 20% of patients have a bloodstream infection.(2, 3) Bacterial pathogens are considered as early causes of infections in this population whereas fungal pathogens and viruses are common causes of later infections.

The risk of fungal infections in febrile neutropenic patients who have undergone chemotherapy, radiation and bone marrow transplantation (BMT) increases as the length of neuropenia increases. In practice, there are a number of antifungal agents as prophylactic or empiric treatments against fungal infections which include "-azole" family like fluconazole and voriconazole, echinocandins like caspofungin and micafungin, and the class of amphotericins including conventional formulation

of amphotericin B, liposomal formulation and lipid soluble formulation of amphotericin.(4)

Amphotericin B which binds to ergosterol in fungal cell membrane causes the membrane alteration, cytoplasmic leakage and cell death. This fungicidal agent may induce nephrotoxicity and electrolyte imbalance so appropriate initial dose and dose adjustment would be helpful to minimize the adverse effects and toxicities.

In this study we run a drug utilization review (DUR) for amphotericin B in the adult patients who have undergone BMT.

Methods

We conducted a prospective observational study at the Hematology-Oncology and Bone Marrow Transplantation Research Center/Tehran University of Medical Sciences (Shariati hospital). The population from which the participants of the present study were drawn included 54 patients admitted to the adult BMT wards. The charts were reviewed by the staff pharmacists on daily basis for the six-month period. The evaluation forms were developed to ease the data collection based on patients' demographic data, including age, gender, reason and type of transplantation, length of hospital stay, antimicrobial regimen during the hospitalization,vital signs (temperature, blood pressure), kidney function (serum creatinine, creatinine clearance), white blood cell (WBC) counts, microbiology tests including cultures, amphotericin B initial dose, further dose adjustment, duration of treatment, also administration data like amphotericin concentration, pre-medication, pre-hydration, adverse drug reactions related to the infusion or other toxicities including nephrotoxicity and electrolyte imbalance. We also utilized criteria from national comprehensive cancer network (NCCN) for justification of the treatment with amphotericin B (e.g., febrile neutropenia at the time of treatment initiation, positive galactomannan test, febrile after 5 days of antibacterial treatment and prophylaxis with fluconazole).(4)

Results

Fifty four patients in three adult BMT wards were evaluated. The most common reasons for transplantation were acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and thalasemia, 20.4%, 18.5% and 16.7% of all cases respectively. In our study, the majority of the patients were males (64.8%), in the age group of 20 to 40 years (50%). Table-1 shows the demographic data of 54 patients included in the study. Regarding administration of amphotericin B, the only diluents used was dextrose 5% in water solution with the final concentration of 0.1mg/ml which was compatible with pharmacy references (e.g., American Pharmaceutical Association drug information handbook).(5) Patients hospitalized in all three wards were premedicated with 50 mg intravenous hydrocortisone and a volume between 3-4 litter intravenous fluids as the routine daily hydration .But only in one ward, patients received normal saline contained potassium chloride and magnesium sulfate as pre-hydration before each dose of amphotericin B. Regarding the dosing, 70.4% of initial doses were appropriate whereas 22.2% of the treatment courses initiated with inappropriate dose or inadequate dosing regimen based on renal function indicators. Through the course of treatment, 27.8% of patients had an increase in their serum creatinine while only 3.7% of cases had dose reduction.

According to criteria for evaluation of amphotericin B indications and regarding the nationwide unavailability (highly expensive if any) of intravenous fluconazole to be used as prophylactic treatment in patients with severe mucusitis, nausea and vomiting and also graft versus host disease (GVHD), we found that 92.6% of patients justified utilization, while 7.4% of cases were identified as an inappropriate treatment. Of all cases, 50% of treatments were prophylaxis versus 42.6% empiric treatment courses. Table-2 shows the treatment justification criteria data. The relationship between initial diagnosis and febrile neutropenia is demonstrated as a bar chart in figure 1.

Discussions

Based on the definition of febrile neutropenia in infectious diseases society of America (IDSA) guidelines, fever is defined as a single temperature of $\geq$38.3˚C or sustained temperature of $\geq$38˚C for $\geq$1 hour. A neutrophil count of <500 cells/mm^3 is defined as neutropenia. The lower the neutrophil count and the longer the duration of neutropenia, the higher the risk of infections.(6) Fungal infections are usually secondary after using courses of antibacterial treatment. Studies have shown that about 30% of febrile neutropenic patients who are not responsive to 5-7 days of broad spectrum antibacterial treatments have a systemic fungal infection, mostly caused by Candida or Aspergillus species.(7, 8) Also when the gastrointestinal (GI) mucosa is damaged due to high doses of

chemotherapy or GI- GVHD, patients become predisposed to blood stream Candida infections.(9) Amphotericin B is an effective option with a broad coverage of both Candida and Aspergillus species (except for Aspergillus tereus which is resistant to amphotericin), although the utilization of its conventional formula is limited due to renal toxicities. Walsh et al, showed the non-inferiority efficacy of liposomal formula and fewer adverse effects in comparison with conventional amphotericin.(10) In two separate studies conducted by Eriksson et al, and Spiech et al, the teams evaluated the tolerability of 24- hour infusion of conventional amphotericin B and both found the continuous infusion as safe and effective treatment against fungal infections.(11, 12) It is recommended to keep the patient well hydrated during the course of amphotericin therapy to minimize its nephrotoxicity and use pre-medications (steroids, acetaminophen and antihistamines) to minimize its infusion-related adverse reactions.(5) Due to more benign adverse drug reaction profiles of fluconazole and echinocandins (caspofungin, micafungin and anidulafungin), the use of such antifungals are practically seen more common than conventional amphotericin B for either prophylaxis or empiric treatments in neutropenic patients.(13) In fluconazole-treated patients with persistent febrile neutropenia, switching to amphotericin B as empiric therapy seems to be reasonable since the occult fungal infection would be due to fluconazole resistant species.(10) The recommended prophylactic dose of conventional amphotericin B is 0.1 to 0.25mg/kg while the dose of empiric treatment is 0.6 to 1.5 mg/kg. Routine monitoring of renal function and serum electrolytes as well as dose adjustment of amphotericin B if necessary seems to reduce the nephrotoxicites.

Conclusion

As the results of this current study showed, the utilization of amphotericin B either as prophylaxtic or empiric treatment was justified in majority of cases (92.6%) with 50% of cases as prophylactic therapy. Since the average course of therapy is over a week for the majority of patients, it is crucially important to monitor and adjust the renal function and amphotericin dose, respectively. Also, it seems necessary to develop a uniform protocol for both hydration and pre-medication while using this antifungal agent to minimize the infusion-related adverse drug reactions.

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