AmBisome: an overview of current use

Han Myint

Although amphotericin B has been the gold standard in treating systemic fungal infections, its use is limited by side-effects including nephrotoxicity. In contrast the empiric or therapeutic use of AmBisome is better tolerated, with less nephrotoxicity.

Amphotericin B has been the gold standard for treating systemic fungal infections in immunocompromised patients for 30 years, because of its activity against a wide range of fungi. It is, however, associated with severe adverse reactions including nephrotoxicity which may compromise its efficacy in treatment. Packaging of amphotericin B in various lipid formulations enables the delivery of a higher dosage to the target tissues with fewer systemic side-effects.

In the last few years, new formulations of amphotericin B have become available which clearly demonstrate significantly improved toxicity profiles and allow significantly higher doses to be tolerated in clinical practice. The most frequently studied of these is liposomal amphotericin B (AmBisome®, NeXstar Pharmaceuticals, Boulder, Colorado), with a number of trials showing the efficacy and safety of AmBisome.

THE NEED FOR ANTIFUNGAL DRUGS

Invasive fungal infections remain a significant cause of morbidity and mortality in immunocompromised patients. Fungal infections can be caused by a wide spectrum of species, the most common being *Aspergillus* and *Candida*, occurring commonly in the environment. Fungi are rarely as invasive or pathogenic as many bacteria or viruses in the normal immunocompetent host, but are opportunistic pathogens, infecting the seriously ill, the very young, and above all the immunosuppressed patient (e.g. cancer patients, bone marrow transplant recipients, leukaemics, acquired immunodeficiency syndrome (AIDS) patients).

As a result, certain risk factors are required for the development of invasive fungal infection, e.g. prolonged and severe neutropenia for the development of *Aspergillus* infection. Furthermore, the duration of neutropenia is directly correlated with an increase in the incidence of invasive aspergillosis. For example, the rate of invasive pulmonary aspergillosis increases progressively after the 6th day of neutropenia at a rate of 1% per day. The rate increases to 4.5% per day between the 24th and 36th days of neutropenia (Gerson et al, 1984). Corticosteroid therapy is another risk factor for *Aspergillus* infection as it suppresses the monocyte–macrophage system, resulting in impaired killing of *Aspergillus* spores by macrophages and impaired mobilization of neutrophils around the fungus.

Other risk factors in developing fungal infections in immunocompromised patients include indwelling catheters, broad spectrum antibiotics, cytomegalovirus infections and environmental exposure. A well-established risk factor for the acquisition of *Aspergillus* infections, especially in bone marrow transplant units, is building work in the hospital environment. Although the inhalation of *Aspergillus* spores is accountable for the majority of cases, the endogenous reactivation of latent organisms may play a role.

Fungal infections can affect almost any organ of the body, are generally characterized by problems in diagnosis and are frequently refractory to treatment. Even where the infecting organism is susceptible to an antifungal agent in vitro, therapy in the very ill and immunosuppressed patient can be difficult, requiring prolonged treatment.

Early diagnosis and prompt antifungal therapy are essential, since the mortality rate in

Dr Han Myint is Consultant Haematologist and Head of Blood and Marrow Transplant Unit, Department of Haematology and Oncology, Royal Bournemouth Hospital, Bournemouth BH7 7HW

patients with invasive aspergillosis is as high as 94% (Denning and Stevens, 1990). The azoles currently available, e.g. fluconazole and itraconazole, are an important group of synthetic antifungal agents, but they are only fungistatic.

This is seen by many as a major drawback, as clearance of the infection is thus highly dependent on the host defence mechanisms. Where these are impaired, the infection frequently cannot be resolved. Although new antifungal agents including newer azoles, echinocandin, pradimicin and nikkomycin are currently undergoing animal and human studies, amphotericin B, either in conventional formulation or lipid-based formulations, is the only option available for clinical use in these patients.

AMPHOTERICIN B

Amphotericin B is a naturally occurring polyene antibiotic, produced by the soil streptomycete *Streptomyces nodosus*, which was discovered in 1955. It consists of a 16-membered macrolide ring, one side being hydrophobic and the other hydrophilic. It has a broad spectrum of antifungal activity and is fungicidal against many of the susceptible species. It is highly insoluble in aqueous media and the clinical preparation is a colloidal dispersion in deoxycholate salts which has to be administered as a slow infusion. The compound suffers from a number of drawbacks (Gallis et al, 1990). These include:

- Infusion-related problems (fever, chills, nausea, vomiting)
- Cardiorespiratory problems (hypotension, hypertension and arrhythmias)
- Kidney toxicity (hypokalaemia, increased creatinine).

A number of studies have shown the failure of prevention of fungal infection by intravenous amphotericin B, in patients at very high risk of contracting fungal infections (Gubbins et al, 1998).

The mode of action of amphotericin B is still not completely understood, even after over four decades of study, but it is clear that the compound interacts with eucaryotic cell membranes. It inserts into the membrane bilayer and associates with the sterols (ergosterol in fungal cells and cholesterol in mammalian cells), causing the formation of pores and disruption of the integrity of the membrane. The disruption is concentration and time dependent, and leads initially to a loss of potassium ions, and subsequently to the leakage of other cell constituents. Additional effects recognized more recently include lipid peroxidation, oxidative damage and inhibition of a range of cellular enzymes (Bratjburg et al, 1990). This multifaceted mode of action is probably why resistance to amphotericin B develops very rarely in fungi.

Although amphotericin B interacts with mammalian cells, its affinity for cholesterol is far lower than that for ergosterol, and this forms the basis of its selectivity for the fungal cell.

LIPOSOMES

The propensity of certain phospholipids to associate into a bilayer in the presence of water was first described by Bangham and Horne in 1964. These bilayers have a tendency to form a vesicle, and the term liposome has been applied to them. Varying types of liposomes can be produced: small unilamellar vesicles, multilamellar vesicles and large unilamellar vesicles.

Following their description, there was considerable interest in the possibility of using liposomes as a means of drug delivery, especially for toxic compounds (Gregoriadis, 1991), but soon the problems in dealing with them became evident. As an experimental tool, they have been widely used, but their commercial exploitation was hampered for many years by instability and difficulties in the production of a uniform product (Gray and Morgan, 1991; Hillery, 1997). Following intense efforts most of these problems have been overcome and recently a number of liposomal preparations have been marketed, with several others undergoing clinical trials. These include preparations for fungal infections, cancer and Kaposi's sarcoma (Hillery, 1997).

A drawback to all liposomal preparations is their high cost compared to the conventional drug. This cost, however, is often offset by the advantages of reduced toxicity, targeting of the drug to the desired site and the ability to give higher doses of the drug.

AMBISOME

AmBisome is a small unilamellar liposomal preparation in which amphotericin B is associated noncovalently with a pure phospholipid bilayer. The pharmacokinetics of AmBisome differ from those of amphotericin B, with a high peak serum concentration and area-under-the-curve, but a relatively short half-life (Coukell and Brogden, 1998). The liposomes are stable in plasma and this is believed to be a key feature of the markedly reduced toxicity of AmBisome. Distribution to deeper compartments is rapid, and it is believed that as lipo-

somes are larger than amphotericin B particles, renal clearance is lower and this contributes to the reduction in renal toxicity (Jankegt et al, 1992; Heinemann, 1994). The liposomes have been shown to localize in infected tissues, where they associate with fungal cells, causing disruption of the liposome and then release of the amphotericin B (Adler-Moore et al, 1993; Adler-Moore, 1994).

THE USE OF AMBISOME IN NEUTROPENIC PATIENTS

The importance of early empiric treatment for fever in neutropenic patients has been emphasized frequently. The predominant pathogens were formerly Gram-negative bacteria, but these have been overtaken by Gram-positive bacteria in recent years, with a significant number of fungal infections also occurring.

Fungi may be the initial cause of the fever in approximately 5% of patients, or may co-exist with bacterial pathogens (Gaya, 1998). The presence of fungi is extremely difficult to detect whether there are mixed infections or not, often only becoming evident when the fever is unresponsive to broad spectrum antibiotics or when fever recurs after an initial response to antibacterial treatment. The risk of fungal infections increases with the degree and time of neutropenia (Gerson et al, 1984; Kelsey, 1996; Gaya, 1998; Richardson and Kokki, 1998).

AmBisome has been used for the empiric treatment of febrile neutropenia in a number of trials and has proved to be far better tolerated and to produce fewer signs of nephrotoxicity than amphotericin B. It has also been shown in a number of recent trials to have greater efficacy than amphotericin B. Prentice et al (1997) used AmBisome at 1 mg/kg/day and 3 mg/kg/day in comparison with amphotericin B at 1 mg/kg/day in two prospective trials involving 204 neutropenic children and 104 adults. The study was primarily designed to determine the comparative safety of the formulations, and results showed quite clearly that there was an almost complete absence of severe adverse events with AmBisome (1% incidence *vs* 12% with amphotericin B). There were also significantly fewer ($P<0.01$) adverse events overall with AmBisome. Nephrotoxicity was significantly reduced in both AmBisome groups ($P<0.01$), even in patients who were receiving other nephrotoxic drugs concomitantly. The overall clinical response to AmBisome at both dose levels was better than that seen in the amphotericin B group. Although there was no significant difference between the 1 mg and 3 mg dosages of AmBisome compared to conventional amphotericin B there was a significant difference between the 3 mg dose and conventional amphotericin B ($P=0.03$).

Another recent study compared AmBisome 3 mg/kg/day with amphotericin B 0.6 mg/kg/day in 687 neutropenic patients, approximately half of whom had received bone marrow transplants (Walsh et al, 1999). Toxicity was far less in the AmBisome patients, with the incidence of fever and chills following infusion being <20% compared with >40% in the amphotericin B group (*Table 1*). Nephrotoxicity was also significantly higher following amphotericin B administration ($P<0.001$). Although the composite success rate for AmBisome was equivalent to that of conventional amphotericin B and the survival rates were not different between the two treatment arms, less proven invasive fungal infection emerged in the AmBisome arm.

Leenders et al (1998) used a higher dose of AmBisome (5 mg/kg/day), but still found a reduction in toxicity with fewer patients having infusion-associated fever and chills. Nephrotoxicity, defined as a creatinine level greater than double that at baseline, was considerably reduced in the AmBisome group, occurring in only 6/52 patients in contrast to 22/54 patients on amphotericin B ($P<0.001$). A favourable trend was seen in those patients with pulmonary aspergillosis treated with AmBisome. The overall mortality rate in the AmBisome group, when adjusted for the malignancy status, was significantly lower; 7/32 in contrast to 13/34 in the amphotericin B group ($P=0.03$). The authors concluded that AmBisome at 5 mg/kg/day was superior to amphotericin B at 1 mg/kg/day both in terms of efficacy and safety.

OTHER USES OF AMBISOME AND PHARMACOECONOMICS

AmBisome has been used successfully in some difficult therapeutic conditions, such as salvage

TABLE 1.
AmBisome *vs* amphotericin B in the empirical treatment of persistently febrile neutropenic patients (*n*=687)

	AmBisome 3 mg/kg/ 24 hours (*n*=343)	Amphotericin B 0.6 mg/kg/ 24 hours (*n*=344)
Survival	93%	90%
Resolution of fever	58%	58%
Rigors/chills	18%	54%
Infusion-related fever	17%	44%
Cardiorespiratory events	13%	45%
Nephrotoxicity	19%	34%

From Walsh et al (1999)

therapy in patients who cannot tolerate amphotericin B or who have already failed on treatment with amphotericin B (de Marie et al, 1994; Coukell and Brogden, 1998). AIDS patients with *Cryptococcus* infections, including those with meningitis, have responded well to AmBisome (de Marie et al, 1994; Leenders et al, 1997; Ringden et al, 1997; Coukell and Brogden, 1998).

Neonates, including those of very low birth weight, and children with a range of fungal infections have been treated with AmBisome (Prentice et al, 1997; Ringden et al, 1997; Coukell and Brogden, 1998; Namdar et al, 1998). The infections that have responded to AmBisome include those caused by *Aspergillus*, *Candida*, *Cryptococcus*, *Curvularia*, *Fusarium*, *Histoplasma*, *Mucor* and *Rhizopus* (Coukell and Brogden, 1998; Namdar et al, 1998).

The high cost of a liposomal preparation may be balanced by the saving in lives of seriously ill patients and the reduction in hospital stay (de Marie et al, 1994; Kelsey, 1996).

CONCLUSIONS

The liposomal preparation of amphotericin B, AmBisome, is now well established as a safer alternative to conventional amphotericin B, being well tolerated and producing very little nephrotoxicity, even when patients are receiving other nephrotoxic drugs concomitantly. It has been shown to be efficacious in the treatment of febrile neutropenia, in the treatment of neonates and children, and also in patients with proven fungal infections, including those caused by *Candida*, *Mucor*, *Aspergillus* and *Cryptococcus*. Although the cost is higher than that of amphotericin B, this can often be balanced by a shortened stay in hospital, reduced toxicity and reduced nursing costs, making it a cost-effective alternative. HM

KEY POINTS

- AmBisome is a liposomal preparation of amphotericin B that can be administered via a peripheral vein over a shorter infusion time than amphotericin B.
- AmBisome is far less nephrotoxic, allowing higher doses to be used safely.
- Acute toxic reactions (infusion related and cardiorespiratory effects) are greatly reduced.
- It has been shown to be safer and at least as effective as amphotericin B in the treatment of pyrexia in neutropenic patients.
- A wide range of fungal infections have been treated successfully with AmBisome.
- It can be used safely in neonates and children over a wide range of doses.

Conflict of interest: None

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