Miltefosine: First Oral Drug for Treatment of Visceral Leishmaniasis

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Introduction

Visceral leishmaniasis (VL) or kala-azar is caused by *Leishmania donovani* and transmitted to humans by female phlebotomine sandflies. Leishmaniasis is distributed worldwide infecting 12 million people, with about 1.5 million new cases each year. Along with Brazil, Sudan and Bangladesh, India contributes to 90% of the global burden of VL [1]. Soon National Leishmaniasis Control Programme in India may have a new drug to fight VL - miltefosine. Miltefosine (Impavido®) is the first oral drug for leishmaniasis, giving cure rates of 98%. The drug can be administered orally and has the potential to be used at the community level and even during an epidemic [2].

Conventional therapy for VL

Conventional therapy for VL consists of parenteral pentavalent antimony (sodium stibogluconate and meglumine antimoniate), given for 28 days (20 mg/kg/day). Severe adverse reactions such as pancreatitis and cardiac toxicity have limited its use. Relapse is common and resistance to antimony is alarming (about 50%).

Discovery of Miltefosine

Miltefosine (1-O-hexadecylphosphocholine), an alkylphosphocholine and a membrane-active synthetic ether-lipid analogue was originally developed and tried for the management of cancer patients. The dose required for such treatment had pronounced side-effects, limiting its usefulness. Simultaneously, in vitro studies showed that it had striking activity against *Leishmania donovani* and *L. infantum*. The results of Phase III clinical trials of miltefosine in India have shown that this oral drug is effective for treating VL in both adults and children, and has limited side-effects [3]. Similar analogues like edelfosine, and ilmofosine are more active than the miltefosine against promastigotes

and intracellular amastigotes of *L. amazonensis* in some of the studies but they are under trial.

Mechanism of action

The molecular mechanisms that contribute to the antileishmanial activity of miltefosine are still unknown. In laboratory studies it was observed that in wild-type promastigotes of *Leishmania donovani*, miltefosine is able to induce a cell death process with numerous cytoplasmic, nuclear, and membrane features of metazoan apoptosis, including cell shrinkage, DNA fragmentation into oligonucleosome-sized fragments, and phosphatidylserine exposure. The activity of miltefosine is attributed to interaction with cell signal transduction pathways and inhibition of phospholipids and sterol biosynthesis [4]. Miltefosine does not appear to kill *L. donovani* promastigotes by direct toxic mechanism.

Pharmacokinetics

Miltefosine is well absorbed after oral administration and is widely distributed. It has a long half-life of about 8 days. Little pharmacokinetic data is available in human beings. In rat, miltefosine is rapidly taken up and accumulates in several internal organs, such as kidney, liver, lung, spleen and adrenal glands. Miltefosine is degraded slowly in vivo, with half-life of 96 hours in mice. It is slowly metabolized by phospholipase to form products such as choline and long chain alcohols that are physiological metabolites and can be recycled into phospholipids [5].

Dosage Schedule and Efficacy of Miltefosine

The dose of miltefosine is 2.5 mg/kg/day orally for 28 days both for children and adult [3, 6]. Currently miltefosine (Impavido) is registered in India and marketed by German Remedies, Ltd. Cost of drug is Rs. 2500 to 5000 per treatment depending on dosage.

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The efficacy of drug was 94% to 97% for children at the end of 6 months on follow up by density of parasites in bone marrow and/or splenic aspirates in phase III trial. Efficacy of miltefosine compares well with other agents, including amphotericin B and liposomal amphotericin B [3]. Hospitalisation for prolonged periods, high cost, requirement of close monitoring and high incidence of adverse events (occasionally serious) are important hindrances in the use of amphotericin B and have prevented its usage at the primary health care level. Amongst all lipid preparations of amphotericin B, Ambisome has the best safety profile. Unfortunately cost of Ambisome is very high (Rs 75000 to 100000) per treatment.

Toxic Effects of Miltefosine

In various clinical trials, toxic effects associated with miltefosine have been tolerable and reversible although therapeutic window appears to be narrow. Gastrointestinal symptoms such as vomiting (38 %) and diarrhoea (20 %) have been brief and of mild to moderate severity in phase III trial. Some patients have reversible hepatotoxicity (15%) and nephrotoxicity (16%) as evident by raised ALT, AST, urea and creatinine which usually gets normal by the end of second week of therapy [7]. Results of phase III trial suggested that oral miltefosine is safe, effective and well tolerated by children with VL in doses used in the study [6].

Phase IV Trial of Miltefosine

A Phase IV trial of miltefosine is now going on in public and private clinics throughout Bihar state. The trial will provide information required before the drug can be included in the kala azar elimination programme in India. The trial will involve 1200 patients, with a 6-month follow-up for efficacy and safety and a 1.5-year follow-up for male reproductive function.

Conclusion

The availability of an oral anti-leishmaniasis drug may revolutionize treatment and control of kala-azar in affected countries. *L. donovani* has acquired resistance to several antileishmanial compounds and the limited experience with miltefosine in HIV co-infected VL patients indicates appearance of resistance to miltefosine, it is important to devise strategies to protect the newly developed drugs from losing their efficacy in the same way as antimony compound. Combination chemotherapy with multiple drugs, as in malaria or tuberculosis, needs to be tested and brought to practice if the life and utility of the new drugs are to be prolonged.

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