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Review Article

Miltefosine: a breakthrough in treatment of leishmaniasis

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Abstract The emergence of leishmaniasis strains resistant to pentavalent antimonials and the growing incidence of leishmaniasis among AIDS patients have made the availability of an oral agent extremely important for management of this disease. Miltefosine (hexadecylphosphocholine), an alkylphosphocholine, is an oral antiprotozoal drug that has recently been hailed as the first oral drug for the treatment of leishmaniasis, with the added advantage of being effective in patients, who had not responded to the standard antimonial drugs. It was initially developed as an oral drug for the treatment of cancer. Present article is an attempt to review different pharmacodyanamic, pharmacokinetic and therapeutic aspects of this new drug.

Key words
Miltefosine, leishmaniasis, anti-leishmanial drugs, anti-protozoal drugs.

Background

Drugs remain the most important tool for the treatment and control of both visceral and cutaneous leishmaniasis. Standard therapy for cutaneous leishmaniasis has been Antimony compounds.[1] These compounds have the disadvantage of being toxic and show clinical resistance in certain regions where they have been used for a long time. Common adverse effects related to these were myalgias, arthralgias, increase in liver enzymes, arrhythmias and repeated parenteral injections.[1-3] There have been several advances in the past decade, with the introduction of new therapies like liposomal amphotericin, paromomycin and oral miltefosine. Miltefosine has recently been claimed to be effective in patients, who had not responded to standard antimonial drugs. The drug is established as first line oral treatment in visceral leishmaniasis but clinical trials in cases of Old World cutaneous leishmaniasis are still underway. It was initially developed as an oral drug for the treatment of cancer. It is currently available as a topical formulation for treatment of certain forms of cutaneous cancer in Europe. The anti-leishmanial activity of this compound was first described *in vitro* and *in vivo* in 1987 and the oral activity in rodent models of visceral leishmaniasis was reported in 1992. The first reports on clinical trials for the treatment of visceral leishmaniasis (VL) in India, supported by ASTA Medica and WHO, came in 1998. Cure rates achieved were up to 98%. Dosage required for treatment of VL was far less than that required in cancer patients, reducing adverse reactions. The mechanism of action of miltefosine on tumour cells has been explored in the past 15 years, but studies on anti-leishmanial mechanisms are limited.[4-10]

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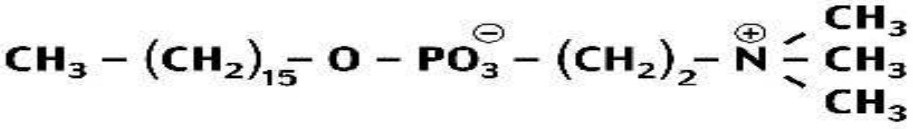

Figure 1 Chemical structure of miltefosine.

Structure

Miltefosine (hexadecylphosphocholine) is a phosphorylcholine ester of hexadecanol, a membrane-active, alkylphospholipid. The chemical structure of the compound is shown in **Figure 1**.

Mechanism of action

Miltefosine (hexadecyl phosphocholine) primarily interferes with cellular membranes without interacting with DNA. It modulates cell membrane permeability, membrane lipid composition, phospholipid metabolism, and mitogenic signal transduction, resulting in cell differentiation and inhibition of cell growth. It also induces apoptotic cell death. As an immunomodulator, miltefosine stimulates T-cells, macrophages and the expression of interleukin 3 (IL-3), granulocyte-macrophage colony stimulating factor (GM-CSF), and interferon gamma (INF-gamma). Unlike other chemotherapeutic agents, miltefosine lack bone marrow toxicity and even exert growth stimulating effects on hemopoeitic progenitor cell. Miltefosine has recently shown strong antileishmanial activity.[11-13]

a) Anti-leishmaniasis action

Miltefosine acts on key enzymes involved in the metabolism of ether lipids (present on the surface of the *Leishmania* parasites). These enzymes include diethylacetonephosphate acetyltransferase, sn-l-acyl-2-lyso-glycero-phosphocholine and sn-l-alkyl-2-lyso-glycero-3-phosphocholine acyltransferase. The initating steps in the ether lipid metabolism occur in glycosomes. Miltefosine inhibits this glycosomal alkyl-specific-acyl CoA acyltransferase in a dose dependent manner.[14] Miltefosine also stimulates *(in vitro)* T cells and macrophages to secrete activating cytokines, including interferon (IFN)- gamma and enhances macrophage production of microcidal reactive nitrogen and oxygen intermediates. To determine these effects *in vivo* genetically deficient mice were infected with *Leishmania donovani*. Intracellular killing was retained in T cell deficient mice suggesting that miltefosine induced visceral leishmanicidal effect does not require host T cell-dependent or activated macrophage- mediated mechanisms.[15]

b) Anticancer action

Miltefosine was originally discovered and synthesized as an anti cancer agent. Its action is exerted at the plasma membrane level, where it interferes with mitogenic signal transduction pathways. Malignant cells are highly sensitive to the lethal action of miltefosine; while normal cells remain relatively unaffected, illustrating the potential anti-tumour properties of the drug. Moreover, miltefosine induces apoptosis in various tumour cell lines and in combination with other anticancer regimens cause additive cytotoxic effects.[11,16]

Pharmacokinetics

After oral administration, miltefosine is well absorbed and is widely distributed. It has a long half-life of about 8 days. However, 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. On oral administration of miltefosine 30 mg/kg of body weight twice per day, concentrations of 155 to 189 nmol/g of tissue are achieved. 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.[15,17-19]

Therapeutic indications

1. Visceral leishmaniasis

Orally administered miltefosine is an effective modality of treatment of Indian visceral leishmaniasis including antimony resistant cases and visceral leishmaniasis with HIV co-infection.[17,20,21] Topical treatment with miltefosine has been shown to efficiently reduce parasite load in experimental cutaneous leishmaniasis.[22] Intracellular visceral infection is suppressed by once or twice weekly orally administered miltefosine in T cell- deficient nude mice infected with *Leishmania donovani*. This supports the usefulness of miltefosine as oral maintenance therapy for T cell deficient patients with visceral leishmaniasis.[15]

2. As an anticancer agent

Skin metastasis of breast cancer has been treated with 6% miltefosine applied locally once daily in the first week and twice daily the following week, with significant reductions in the lesions.[23]

3. Other potential indications

I. Anti-leishmanial; Preliminary results have shown a great potential in cases of cutaneous leishmaniasis.[4,5,9,22]
II. Amoebicidal; *Entameoba histolytica*, could be a possible new target.[18]
III. Anti-trypnosomal; *Trypanosoma cruzi* and *T. brucei*, are other possible targets.[14]
IV. Anti-leukemic; Miltefosine is potent inducer of apoptosis and displays increased antileukemic efficacy against BCR-ABL-positive blasts.[23]
V. Human urinary bladder & head and neck tumors; Miltefosine potentially could prove to be of benefit for patients with urinary bladder neoplasia and head and neck tumors.[24,25]
VI. Metastatic solid tumors: Its use has been evaluated in squamous cell cancer and number of metastatic solid tumors.[25,27] However, more studies are required to prove its efficacy.

Dosage schedule and efficacy

The dose of miltefosine for the treatment of visceral leishmaniasis is 2.5 mg/kg/day preferably in two divided doses or single dose orally for 28 days; the dose should be adjusted based on patients weight so that a dose of 4mg/kg per day is not exceeded. The recommended dose for the treatment of cutaneous leishmaniasis is the same as in visceral leishmaniasis. The drug is available as 50 mg and 10 mg capsule/ tablet (Asta Medica, Frankfrut, Germany). The efficacy of drug was 94% and 97% for children at the end and at 6 months respectively on follow up calculated by density of parasites in bone marrow and/or splenic aspirates in phase 3 trial. Hence efficacy of miltefosine compares well with other agents, including pentavalent antimonials, amphotericin B and liposomal amphotericin B.[12,17,21]

Contraindications

It is contraindicated in women with child bearing potential because of its teratogenic effects in animal studies.[12,21]

Drug resistance

The resistance to anti-kala-azar drug is a major problem. Hanson *et al.*[13] identified mutation in a single gene YNL 328 W/LEM 3 that conferred resistance to alkyl phosphocholine including miltefosine in *S. cerevisae* and inhibited internalization of NBD-labelled phosphocholine and phosphatidyl ethanolamine. They also concluded that lem 3p expression is essential for uptake and potency of miltefosine. Perez-Victoria *et al.*[28] also demonstrated defective translocation of miltefosine by resistant *L. donovani* promastigotes. They also observed miltefosine uptake to be temperature and energy dependent and sensitive to thiol reactive agent, N-ethylmaleimide.

Toxic effects

Miltefosine is well tolerated with considerably fewer adverse effects as compared to antimonials and amphotericin. In various clinical trials toxic effects associated with miltefosine have usually been found to be reversible although therapeutic window appears to be narrow. Gastrointestinal symptoms such as vomiting (38 %) and diarrhoea (20 %) although common, have been brief and of only mild to moderate severity in phase 3 trial. Some patients have reversible hepatotoxicity (15%) and nephrotoxicity (16%) as evidenced by raised ALT, AST, urea and creatinine which usually become normal by end of second week of therapy. Gastrointestinal symptoms could be significant in severely ill patients such as those who are malnourished and dehydrated. Miltefosine though used as an antineoplastic agent is devoid of hematological toxicity. Pregnancy is a contradiction to the use of miltefosine because it is teratogen to animals.[12,29-32] The availability of miltefosine for treatment of VL is an important breakthrough in management of this disease. All other agents that are recognized as effective are potentially toxic and parenteral. Hence miltefosine should be used as first-line anti-leishmanial drug in treating children with VL and cutaneous leishmaniasis above 2 years of age. There are some questions that are still unanswered regarding miltefosine.[33] Will miltefosine continue to be highly effective and acceptably tolerated when more patients are treated? How broadly applicable will miltefosine therapy be for diversity encompassed by human leishmaniasis?

Conclusion

Oral miltefosine is a highly effective and a well-tolerated drug and is an important breakthrough in management of the disease. By rapid reduction of parasite load the duration of treatment can be reduced and subsequent relapses prevented. Nevertheless, larger controlled phase III studies of miltefosine are required to support these findings. Considering man as the reservoir of the *Leishmania* parasite, it can be expected that miltefosine will play a key role in eradication of visceral leishmaniasis.

References

1. Herwaldt BL, Berman JD. Recommendations for treating leishmaniasis with sodium stibogluconate and review of pertinent clinical studies. *Am J Trop Med Hyg* 1992; **46**: 296-306.
2. Bryceson A. A policy for leishmaniasis with respect to the prevention and control of drug

resistance. *Trop Med Int Health* 2001; **6**: 928-34.
3. Croft SL, Sundar S, Fairlamb AH. Drug resistance in leishmaniasis. *Clin Microbiol Rev* 2006; **19**: 111-26.
4. Croft SL, Seifert K, Yardley V. Current scenario of drug development for leishmaniasis. *Indian J Med Res* 2006; **123**: 399-410.
5. Alvar J, Croft S, Olliaro P. Chemotherapy in the treatment and control of leishmaniasis. *Adv Parasitol* 2006; **61**: 223-74.
6. Sindermann H, Engel J. Development of miltefosine as an oral treatment for leishmaniasis. *Trans R Soc Trop Med Hyg* 2006 May 24; [Epub ahead of print]
7. Berman JD. Development of miltefosine for the leishmaniases. *Mini Rev Med Chem* 2006; **6**: 145-51.
8. Soto J, Soto P. Miltefosine: oral treatment of leishmaniasis. *Expert Rev Anti Infect Ther* 2006; **4**: 177-85.
9. Soto J, Arana BA, Toledo J *et al.* Miltefosine for new world cutaneous leishmaniasis. *Clin Infect Dis* 2004; **38**: 1266-72.
10. Schraner C, Hasse B, Hasse U *et al.* Successful treatment with miltefosine of disseminated cutaneous leishmaniasis in a severely immunocompromised patient infected with HIV-1. *Clin Infect Dis* 2005; **40**: e120-4.
11. Jendrossek V, Handrick R. Membrane targeted anticancer drugs: potent inducer of apoptosis and putative radiosesis. *Curr Med Chem Anti-Canc Agents* 2003; **3**: 343-53.
12. Sunder S, Jha TK, Thakur CP *et al.* Oral Miltefosine for Indian Visceral leishmaniasis. *N Engl J Med* 2002; **347**: 1739-46.
13. Hanson PK, Malone L, Birchmore JL, Nichols JW. Lem 3 p is essential for the uptake and potency of alkylphosphocholine drugs, edelfosine and miltefosine. *J Biol Chem* 2003; **5**: 1324-31.
14. Lux H, Heise N, Klenner T, Hart D, Opperdoes FR. Ether–lipid (alkyl-phospholipid) matabolism and the mechanism of action of ether – lipid analogues in visceral leishmania. *Mol Biochem Parasitol* 2000; **111**: 1-14.
15. Murray HW. Suppression of post treatment recurrence of experimental visceral leishmaniasis in t- cell- deficient mice by oral miltefosine. *Antimicrob Agents Chemother* 2000; **44**: 3235-6.
16. Ruiter GA, Verheij M, Zerp SF, van Blitterswijk WJ. Alkyl-lysophospholipids as anticancer agents and enhancers of radiation-induced apoptosis. *Int J Radiat Oncol Biol Phy* 2001; **49**: 415-9.
17. Jha TK, Sundar S, Thakur CP *et al.* Miltefosine, an oral agent, for the treatment of Indian visceral leishmaniasis. *N Engl J Med* 1999; **341**: 1795-800.
18. Bresiser A, Kim DJ, Fleer EA *et al.* Distribution and metabolism of hexadecylphosphocholine in mice. *Lipids* 1987; **22**: 925-6.
19. Seifert K, Duchaene M, Werndorfer WH *et al.* Effects of miltefosine and other alkylphosphocholines on human intestinal parasite *Entamoeba histolytica*. *Antimicrob Agents Chemother* 2001; **45**: 1505-10.
20. Mohan A, Seth S. Oral miltefosine in treatment of kala azar. *Nat Med J Ind* 2000; **13**:202-3.
21. Thakur CP, Sinha PK, Singh KR *et al.* Miltefosine in a case of visceral leishmaniasis: and rising incidence of this disease in India. *Trans R Soc Trop Med Hyg* 2000; **94**: 696-7.
22. Schmidt-Ott R, Klenner T, Overath P, Aebischer *. Topical treatment with heaxdecylphosphocholine (miltex) efficiently reduces parasite in experimental cutaneous leishmaniasis. *Trans R Soc Trop Med Hyg* 1999; **93**: 85-90.
23. Konstantinov SM, Eibl H, Berger MR. BCR-ABL influences the antileukaemic efficacy of alkylphosphocholine. *Br J Haematol* 1999; **107**: 365-80.
24. Konstantinov SM, Berger MR. Human urinary bladder carcinoma cell line respond to treatment with alkylphosphocholine. *Cancer Lett* 1999; **144**: 153-60.
25. Verweij J, Gandia D, Planting AS *et al.* Phase II study of oral miltefosine in patients with squamous cell head and neck cancer. *Eur J Cancer* 1993; **29A**: 778-9.
26. Verweij J, Planting AS, van der Burg M, Stoter G. A dose finding study of miltefosine (hexadecylphosphocholine) in patients with solid tumors. *J Cancer Res Clin Oncol* 1992; **188**: 606-8.
27. Smorenburg CH, Seynaevec *, Bontenbal M *et al.* Phase II study of miltefosine 6% solution as topical treatment of skin metastases in breast cancer patients. *Anticancer Drugs* 2000; **11**: 825-8.
28. Perez- Victoria FJ, Castanys S, Gamaroo F. *Leishmania donovani* resistance to

miltefosine involves a defective inward translocation of the drug. Antimicrobiol *Agents Chemother* 2003; **47**: 2397-403.
29. Sunder S, Jha TK, Sindermann H *et al*. Oral miltefosine in children with mild to moderate Indian visceral leishmanisis. *Pediatr Infect Dis J* 2003; **22**: 434-8.
30. Prasad R, Kumar R, Jaiswal BP, Singh UK. Miltefosine: an oral drug for visceral leishmaniasis. *Indian J Pediatr* 2004; **71**: 143-4.
31. Beckers T, Voegeli R, Hilgard P. Molecular and cellular effects of hexadecylphosphocholine (miltefosine) in human myeloid leukemic cell lines. *Eur J Cancer* 1994; **30D**: 2143-50.
32. Sundar S, Gupta B, Makharia MK *et al*. Oral treatment of visceral leishmaniasis with miltefosine. *Ann Trop Med Parasitol* 1999: **93**; 589-97
33. More B, Bhatt H, Kukreja V, Ainapure SS. Miltefosine: great expectations against visceral leishmaniasis. *J Postgrad Med* 2003; **49**: 101-3.