CHAPTER 28

# MILTEFOSINE

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Miltefosine is an alkylphosphocholine drug with demonstrated activity against various parasite species as well as cancer cells.[1] It was originally discovered and synthesized as an anticancer agent.[2,3] Miltefosine is the first effective and safe oral agent with the potential to treat all major clinical presentations of leishmaniasis.[4] Alkylphosphocholines have also shown in vitro and in vivo activity against Trypanosoma spp., amoebae, Trichomonas vaginalis, Schistosoma mansoni, HIV, and some fungi and bacteria species.[5]

## Mechanism of action

Miltefosine belongs to the class of alkylphosphocholine drugs, which are phosphocholine esters of aliphatic long-chain alcohols. These alkylphosphocholine compounds are structurally related to the group of alkyl-lysophospholipids, which are synthetic analogues of lysophosphatidylcholines or lysolecithins, but lack their glycerol backbone. Both miltefosine's antileishmanial and antineoplastic features are assumed to be derived from its action on the cell membranes and apoptosis inducing effects.[1]

The mechanism of action of miltefosine is likely to involve interaction with lipids (phospholipids and sterols), including membrane lipids, inhibition of cytochrome c oxidase (mitochondrial function) and apoptosis like cell death.[1,6] Miltefosine inserts into the cell membrane where it generates a biophysical perturbation, interfering with phospholipid metabolism, proliferation and cell survival signaling pathways.[5] *Leishmania* have high levels of ether-lipids and these are mainly found in the glycosylphosphophatidylinositol anchored glycoprotein and glycolipids present on the surface of the parasites. Miltefosine acts on key enzymes involved in the metabolism of ether lipids. The initial steps in the ether-lipid metabolism occur in glycosomes. Miltefosine does not act on the initial steps in ether-lipid metabolism in *Leishmania.* However, the metabolism of latter phosphatidylcholine intermediates which are involved in the synthesis of acyl- and alkyl-glycerophospholipids, are associated with glycosomes. Miltefosine inhibits this glycosomal alkyl specific-acyl CoA acetyltransferase in a dose dependent manner.[7] The interference of miltefosine with the metabolism of cell membranes leads to a cellular stress that in turn, triggers apoptosis.[1,5] Miltefosine is able to induce this programmed apoptosis-like cell death in promastigotes and intra-/extracellular amastigotes of *L. donovani*, and in *Leishmania amazonensis* and *L. infantum* promastigotes.[1]

Miltefosine has also immunomodulatory effects: it induces interferon-γ from macrophages and enhances interferon-γ responsiveness by expressing interferon-γ receptors in macrophages.[8] Th1/Th2 balance is restored by promoting the interleukin-12-dependent Th1 response.[1] Miltefosine's immunomodulary actions may have a role in its antileishmanial activity. Lipid rafts are phospholipid and cholesterol-enriched domains in the cell membranes, which together with raft proteins form localized microdomains. Miltefosine is a derivative of cell membrane phospholipids and is enriched in rafts containing the high affinity receptor for IgE, FceRI. There is a significant evidence demonstrating the inhibition of signal transduction pathways at the level of the cell membrane by miltefosine. Miltefosine has also been shown to be taken up by cells in a raft-dependent fashion, suggesting that it has a high affinity to lipid raft microdomains. It acts as a lipid raft modulator and, thereby, interferes with the response of mast cell activation and degranulation. In vitro tests have demonstrated that miltefosine dose-dependently inhibited anti-IgE induced histamine release from mast cells. TNF release was also inhibited in a dose dependent manner.[9]

Miltefosine mediates its antineoplastic effects through its actions on cell membranes. Miltefosine exerts its cytotoxic action predominantly by interacting with the cell membrane components that are linked to phospholipid turnover and membrane signal transduction. As a result, miltefosine inhibits protein kinase C, which induces cell differentiation.[10] Additionally, miltefosine inhibits phosphocholine synthesis which in turn triggers apoptosis. The mechanism by which the inhibition of phosphocholine biosynthesis initiates apoptosis is not clear. It has been shown that the lack of phosphocholine in the endoplasmic reticulum somehow induces a stress of the pro-apoptotic transcription factor CHOP/GADD 153. Miltefosine also inhibits AKT, a serine/threonine kinase which is a key regulator of various cell survival pathways. AKT is activated in most human cancers and contributes to cell growth,

normalizes in the subsequent weeks together with the resolving infection. Reversible grade III hepatotoxicity and renal damage have also been reported in some cases.[1,2]

When applied topically, local skin reactions are common, including pruritus, burning, erythema, skin dryness and scaling, but these side effects rarely necessitate discontinuation of therapy.[11,47]

**Contraindications**: Animal studies have demonstrated that miltefosine is teratogenic. Therefore, the use of miltefosine is containdicated in pregnant women and adequate contraceptive measures are mandatory for females with childbearing potential during and after treatment. Four months of adequate contraceptive cover after the end of treatment is recommended.[1]

## Summary

Systemic miltefosine is the first recognized oral treatment for leishmaniasis. Miltefosine treatment may be a promising option for patients with multiple or complicated Old World cutaneous leishmaniasis lesions. Miltefosine has been used in the management of New World cutaneous leishmaniasis with variable efficacy. Miltefosine shows comparable results in some studies, although treatment success shows geographic variations, possibly related to differences in parasite strains. It may be a reasonable option for cases with moderate New World mucocutaneous leishmaniasis. Systemic miltefosine may be considered a second-line treatment option for chronic urticaria patients who do not respond to antihistamines; the place of topical miltefosine is investigational in the management of atopic dermatitis and cutaneous mastocytosis. Topical miltefosine is an effective palliative treatment option for patients with skin metastasis from breast cancer and also in certain patients with cutaneous T-cell lymphoma. The potential teratogenic effects of the drug should be taken into consideration.

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