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Short communication

New pharmaceuticals: Miltefosine

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Miltefosine is a new chemical entity which was synthesized by H.J. Eibl at the Max-Planck Institute for Biophysical Chemistry in Göttingen (Germany) and first used clinically in 1988/89 to treat cutaneous breast cancer metastases by G. Nagel and C. Unger, both at the University Hospital in Göttingen (Germany). Studies into the pharmacology and toxicology of the compound were carried out jointly at the German Cancer Research Center in Heidelberg and ASTA Pharma's Cancer Research Laboratories in Bielefeld (Germany).

The structure of miltefosine (hexadecylphosphocholine) is related to the phospholipid molecule, which is the major constituent of the lipid double layer of cell membranes. There is evidence from biochemical studies in isolated tumor cells and from animal experiments that the antitumor activity of this compound is mediated by pharmacological effects at the level of the cancer cell membrane. This suggests that its mode of antitumor action is distinctly different from that of the classical cytostatic drugs which interact with cell proliferation at the level of DNA replication.

Miltefosine exerts major antitumor activity in carcinogen (DMBA, MNU)-induced breast cancers of experimental animals. Its effect is dose-dependent and not only suppresses tumor growth in comparison to controls but also leads to remission of already established large tumors. These experimental cancers are rather insensitive to conventional chemotherapy, and this fact makes miltefosine a particularly interesting therapeutic agent. Bone marrow toxicity, the prevalent side effect of current cancer chemotherapy, does not occur.

Following the induction with the carcinogen dimethyl-benzanthracene (DMBA) in female rats, most tumors will be slowly growing breast cancers with estrogen receptors and histological features similar to those found in human breast cancer. However, a small proportion are rapidly growing, hormone receptor-negative sarcomas. These latter tumors are insensitive to the treatment with miltefosine. In further studies, it was shown that DMBA tumors relapsing after initial hormonal therapy were equally sensitive to miltefosine. Since these relapsed cancers do not respond to a second hormonal therapy, it was concluded that miltefosine does not act via an interaction with cancer cell associated estrogen receptors.

Evidence from sequential histological sections of miltefosine-treated DMBA tumor bearing animals revealed that tumor regression was associated with differentiation of the malignant tissue towards normal, milk-producing breast tissues.

The clinical development of miltefosine has two therapeutic goals: (1) its use as topical, palliative treatment of cutaneous breast cancer metastases and (2) the systemic oral treatment of slow growing tumors. Ongoing phase II studies in Europe have established a substantial palliative effect of a local miltefosine treatment. The dose-finding (phase I) studies for oral systemic therapy are terminated and phase II studies have been initiated to evaluate the therapeutic efficacy of miltefosine in tumors such as colorectal cancer, non-small-cell lung cancer, head and neck cancer, and breast cancer.