GUEST EDITORIAL

Membrane-interactive lipids as experimental anticancer drugs

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Ether lipids and their derivatives represent a new class of compounds for experimental therapy of neoplasia. The activity of these agents is partially mediated through non-specific host resistance cells (Munder et al., 1977). In addition, they possess direct effects on neoplastic cells. They are cytotoxic, anti-invasive and can induce cell differentiation. Although the molecular mechanisms leading to these direct effects are yet poorly understood, accumulation of these agents in neoplastic cells, disturbing lipid metabolism and subsequently destroying cell membranes seems to be crucial for their cytotoxicity. Thus, in the process of developing these new drugs cell membranes have evolved as a target for experimental cancer therapy. Some reviews on the development in this area have been published during the last years (Berdel et al., 1985, 1987; Baumann et al., 1987). This is a brief update of significant new aspects, which could be further exploited experimentally or are important for the clinical development of these drugs.

Preclinical studies

Alkyl-lyso phospholipids (ALP) are analogs of lyso phosphatidylcholine and were originally synthesised as a new class of biological response modifiers (Munder et al., 1977). During an investigation of the influence of ALP analogs on cellular immunity, strong antitumour effects of some of these compounds were observed in the allogeneic Ehrlich ascites tumour in mice (Munder et al., 1977). Further studies showed antimetastatic activity in the anaplastic Lewis lung carcinoma in mice (Berdel et al., 1980). Additional therapeutic screening of the first generation ALP analogs in different laboratories subsequently revealed that a wide variety of murine and rat tumour and leukaemia models is sensitive to the therapeutic activity of these lipids with some other tumour and leukaemia systems being rather resistant to this material (see Berdel, 1990). Some of the compounds, such as the ALP analog ET-18-OCH₃ or the thioether-phospholipid BM 41,440 (see Figure 1) have been also tested for therapeutic activity in xenotransplanted human tumours growing in athymic (nu/nu) mice. Considerable growth retardation of some gynecological tumours was found under systemic therapy with some of these compounds (Runge et al., 1980). However, other xenotransplanted human tumours have been found as being resistant (Leder et al., 1987).

Vogler and co-authors (Glasser et al., 1984; Vogler et al., 1987) demonstrated selective cytotoxic activity of ET-18-OCH₃ in experiments with a mouse model for syngeneic bone marrow transplantation. Lethally irradiated mice were transplanted with normal bone marrow cells containing 1–2% leukaemic cells (WEHI-3B) to simulate a remission marrow after the cells were incubated with various concentrations of ET-18-OCH₃ in vitro. Lethally irradiated mice were transplanted with normal bone marrow cells containing 1–2% leukaemic cells (WEHI-3B) to simulate a remission marrow after the cells were incubated with various concentrations of ET-18-OCH₃ in vitro. All of the mice given cells not treated with ET-18-OCH₃ in vitro succumbed to leukaemia, whereas there was a dose-related increase in survival in those animals transplanted with ET-18-OCH₃-treated cells. Thus, ether lipids seem to be suited for purging residual malignant cells from marrows prior to autologous bone marrow transplantation (ABMT).

During the early treatment studies, it became evident that the antineoplastic activity of some ALP analogs in vivo might be partially mediated by cytotoxic macrophages (Munder et al., 1977; Berdel et al., 1980; Andeenes et al., 1984). Assessing the importance of cytotoxic macrophages as mediators of ALP-effects, it could be shown that macrophages not only are cytotoxic in vitro to a variety of neoplastic cells after incubation with these lipids, but can be also used for successful treatment of syngeneic tumour and metastasis develop-

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**Development of new ether lipids**

With the first generation of ALP analogs and particularly ET-18-OCH₃ as a reference structure, many laboratories have embarked on the chemical synthesis and the screening of a variety of structurally related compounds with possible antineoplastic activity (for further literature see Berdel, 1990). Among structures showing promising in vitro and/or in vivo action are 1-thioether phospholipids, such as BM 41,440, other sulfur-analogues, alkyl-ethylene-glycolphospholipids, 2-acetamide analogues of ALP, 2-alkoxylalkyl- and 2-alkoxylalkenyl-phosphocholines, 1-N-alkylamides of glycerophosphocholine and various non-phosphorus ether lipids. Other structures, such as analogues of platelet activating factor and alkyl-linked lipoidal amines show in vivo antitumour properties. However, some of them, such as the lipoidal amine CP 46,665, have almost no therapeutic range in vivo and thus are not further studied.

Addition of other cytotoxic drugs and other treatment modalities like hyperthermia have been shown to potentiate the cytotoxicity of some other lipids in vitro (Okamoto et al., 1988; Noseda et al., 1988; Fujitawa et al., 1989; Hofmann et al., 1989). These additive or supra-additive effects are currently under further investigation. Interestingly, some of these membrane-active ether lipid structures inhibit infectious HIV-1 production and induce defective virus formation in T-cells (Kucera et al., 1990). This effect is currently under study for combination chemotherapy with DNA-interactive anti-HIV nucleoside analogs.

Based on the hypothesis that degradation of certain ALP analogues by a phospholipase C is required for the generation of toxic metabolites (Fleer et al., 1987), Eibl and co-workers have synthesised derivatives of ether lipids such as a series of alklyphosphocholines (APC). One of the most active APC is hexadecylphosphocholine (D 18506, Asta-Werke, Germany), which is depicted in Figure 1. The investigators showed impressive therapeutic in vivo activity of D 18506 in a breast cancer model in rats (Hilgard et al., 1988). Our recent work has concentrated on chemical conjugates of other lipids and other cytotoxic drugs, such as nucleoside analogs. It could be shown, that sn-3 lipid conjugates of arabinoside-cytosine (ara-C), when tested in vivo in various leukaemia and solid tumour models in mice including xenografts, have a comparably high therapeutic activity (Berdel et al., 1988, 1989; Hermann & Berdel, 1989).

**Clinical studies**

Currently, there are four membrane-toxic lipids in early clinical trials for treatment of cancer and leukaemia. ET-18-OCH₃, the first ether lipid entered into early clinical trials (Berdel et al., 1985), was given to patients with non-small cell lung cancer (NSCLC) per os in a multi-institutional phase II drug efficacy study (Khanavkar et al., 1989). A multi-institutional phase I drug safety trial with BM 41.440 given orally has been recently completed (Herrmann et al., 1989) and this drug has entered phase II drug efficacy trials in a wide spectrum of neoplastic diseases. Hexadecylphosphocholine is currently being studied in a phase II trial for the topical treatment of skin metastases in patients with breast cancer (Unger et al., 1988) and has completed two phase I
Thus, tumour responses in vitro have been observed with some patients remaining with no change of their disease parameters for various times (Khanakvar et al., 1989). Thus, the systemic clinical activity of these drugs as available and as given up to now is marginal and their clinical potential remains doubtful. On the other hand intravenous dose response relations of some ether lipids in vivo are impressive in animal models (Berger & Schmähl, 1987; Herrmann & Bicker, 1988). Hence, better galenic formulation and early clinical trials with parenteral high dose/long time application of some of these ethers is urgently warranted in order to clarify whether the lipids available so far can be exploited as therapeutic agents in clinical oncology.

A clinical phase I/II study to assess the safety and efficacy of bone marrow autotransplantation after supralethal chemotherapy and radiotherapy in patients with acute leukaemia using remission marrows purged with ether lipids in vitro is currently underway (Berdel et al., 1990).

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