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The Recent Research Regarding Alkylglycerols – (Ether Lipids)

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The recent research regarding Alkoxyglycerols - (Ether lipids)

Alkylglycerols (Alkoxyglycerols) constitute in their synthetic form a new family of anti-cancer drugs which target the cell membrane as their site of action. Enzymes involved in signal translation - (protein kinase C and phosphatidylinositol phospholipase C), phospholipid biosynthesis (lysophosphatidyl-acyltransferas and CTP-cholinephosphate cylidyltransferase) and maintenance of membrane integrity (Na, K ATP-ase sodium pump) have been shown to be inhibited by Alkoxyglycerols. Ether phospholipids (Alcyxyglycerols) have been found active against a variety of tumour cell lines, including drug-resistant sub-lines. Particularly the antiproliferative activity of these ether phospholipids ET-18 OCH_3 (Edelfosine), BM 41, 440 (Limofosine) and a new azaderivative (B 52205) have been proved active on three leukaemia cell lines i.e. K 562 (chronic myeloid, leukaemia blast crisis), HL_{60} (promyelolytic acute leukaemia) and CEM (T-cell leukaemia and their respective drug-resistant sub-lines, i.e. K 562-ADR (adryamicin resistant), HL_{60} DNR (daunorubicin (DNR) resistant) and CEM VLB (vinblastin resistant).

Alkoxyglycerols (ET-18 OCH_3) has been recently shown to induce apoptosis in the human leukaemia HL_{60} and U 937 myeloid cell lines (Mollinedo, Martinez - Dalman and Modotell 1993. Biochem. Biophys. Res. Commun. 192, 603-609).

It was also found that ET-18 OCH_3 is able to promote apoptosis in the human leukaemia , Jurkat T lymphoid cell line. It was shown that alkoxyglycerols of this type can induce expression of fos and jun proto-oncogenes by modulating the activity of transcription factor AP-1 (Biochem. J. 1994; 302: 325-329). Alkoxyglycerols (alkyllysophospholipids) are directly cytotoxic to a variety of neoplastic cell lines and can modulate the activation of macrophages against tumour cells. Moreover, recent reports have demonstrated the ability of ET-18 OCH_3 to prevent tumour cell invasion when given in non-cytotoxic concentrations. The anti-invasive effect of this ether lipid (alkoxyglycerols) has been found useful in the treatment of transitional cell carcinoma (J. Urol. 1994; 152: 1594-1598).

Using the spin trap alpha (4-pyridyl-1-oxide) N-tertbutylnitrone it was detected the generation of lipid derived carbon-centred free radicals in the T. 1210 lymphoblastic leukaemia cells.
The oxidative stress is considered to play an important role in the cytotoxic mechanism of this class of anti-cancer drug. (Cancer Research. 1993; 15: 711-713).

A unique feature of the alkylglycerols is their selective cytotoxicity to neoplastic cells. This unique prosperity of alkoxyglycerols suggest that these compounds should be excellent agents for purging residual leukaemia cells from marrow's of patients in remission prior to autologous bone marrow transplantation.
Pre-clinical studies in a leukaemia model and in an in vitro human system demonstrated successful elimination of leukaemia cells from a mixture of normal and leukaemia

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Twenty-nine poor risk patients with acute leukaemia underwent autologous bone marrow transplantation and were re-infused with marrow treated in vitro with alkoxyglycerols edelfosine. Nine of these patients remain in remission free of leukaemia from 368 to 1369 days (Leuk-Lymphoma 1994; 13: 53-60).

All these new reports regarding the anti-tumour activity against different types of cancer of alkoxyglycerols explain and confirm their important physiological role as natural immunostimulators and anti-cancer factors in humans. It is an open question whether a future research should concentrate on the all possible effects of naturally occurring alkoxyglycerols or whether all efforts should be concentrated on the synthesis of a potent chemical analogue - anti-cancer drug of the future.

Interleukin -2- (IL-2) is a potent stimulant of T lymphocytes that induces their receptor presentation on the surface membrane and stimulates cell proliferation (Tan. E.M. Adv. Immunol. 1982; 33: 167-240). T lymphocytes activation and the subsequent cell proliferation are initiated following the binding of Lectin or antigen to cell surface receptors by which turnover of membrane phospholipids takes place. It was recently shown that IL-2 dependent cytotoxic T lymphocytes (CTL) contain a large amount of ether lipids in the membrane phospholipids and that the phospholipids composition can change as a result of IL-2 stimulation (Nishiva, J. Ishibastri T. Saniamura, Y. Hosokawa, M. Biochem, Med. Biol. 1994; 33: 137-146). In a recent study it was shown that ether lipids regulate the physiological functions of CTL (Nishiva, J. Ishibastri, T. Saniamura, Y. Hosokawa, M. Molecular species of phospholipids of Interlenkin-2 dependent murine cytotoxic T lymphocytes. Biochem. Med. Biol. Intern. 1995; 35: 1017-1027).

Successful treatment with ether lipids of natural origin - Alkymer, has inspirited several research groups and pharmaceutical industry to find the synthetic ether lipids mimicking the action of Alkymer.
Thus synthetic anti-tumour lipids (ATLs), including the novel alkylphosphocholines derivatives, have emerged as effective agents in model systems and are currently undergoing clinical trials (Berdel, W.E. Ether lipids and derivatives as investigation anti-cancer drugs. A brief review Onkologic, 1990; 13: 245-250. Berdel, W.E. Membrane interactive lipids as experimental anti-cancer drugs - Brit. J. Cancer. 1991; 64: 208-211. Honlihan, W.J. Lohmeyer, M. Workman. P and Cheon, S.H. Phospholipid anti-tumour agents. Med. Res. Rev. 1995; 15: 157-223).
Current pre-clinical and clinical experience with these agents has recently been comprehensively reviewed (Lohmeyer. M. and Bittman. R. Anti-tumour ether lipids and alkylphosphocholines. Drugs future. 1994; 19: 1021-1037).
They represent a new class of distinct non-DNA interactive anti-tumour agents whose main site of action appears to at the plasma membrane (Diomede. L. Bizzi. A. Magistrelli. A et. Al. Role of cell cholesterol in modulating anti-neoplastic ether lipid uptake, membrane effects and cytotoxicity. Int. J. Cancer 1990; 46: 341-246. Grunidee. H.A. The cell membrane as a target for cancer chemotherapy. Europ. J. Cancer. 1991; 27: 281-284). Similar to Alkymer, in addition to their direct effects on

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tumour cells some ATLs also activate the host immune system (Hilgard. P. Kampherus. E. Nolan. E. et. Al. Investigation into the immunological effects of miltefasine, a new anti-cancer agent under development. J. Lancer. Res. Clin. Oncol. 1991; 117: 403-408. Pignol. B. Chaunerou. S. Lonlamb. H. et. al. Immunomodulatory activity of two new aza alkyl phospholipid anti-neoplastic drugs. Anti-Cancer Drugs. 1992; 3: 599-6089).

The encouraging results obtained in variation model system, wave highlighted the therapeutic potential of ATLs. Several compounds corresponding or mimicking those present in Alkymer are scheduled for, or currently undergoing phase I/II clinical evaluation (Lohmeyer and Bittman, 1994 - see above). Considerable success has already been achieved with bone marrow purging (Bendel, 1991 - see above, Vogler. W.R. Bone marrow purging in acute leukaemia with alkyl - lysophospholipids, a new family of anti-cancer drugs. Lenk. Lymphorna. 1994; 13: 53-60).
The beneficial and surprisingly good results with Algemar topical application inspirited also a corresponding research and trials with synthetic ether lipids.

Topical application of these compounds (for instance - hexadecylphosphocholine - Hc PC) in breast cancer has also produced encouraging results (Dummer. R. Röger. J. Vogt. I. et. al. Topical application of hexadecyliphosphocholine in patients with cutaneous lymphomas. Prog. Exp. Tumour. Res. 1992; 24: 160-169. Unger. C. Sindermann. H. Penkert. M. et. al. Hexadecylphosphocholine in the topical treatment of skin metastases in breast cancer patients. Prog. Exp. Tumour. Res. 1992; 34: 153-159).

Various studies suggest that ATLs inhibit cell growth of sensitive HT29 and HL60 cancer cells in a fashion which involves three distinct phases depending on ATL concentration. At low doses of ATL effect a gradual cessation of population growth (Cytostasis). The ATLs induce cytostasis in HL60 cells without concomitant cellular differentiation.

At intermediate concentration a net reduction of viable cancer cell number is observed (cytotoxicity) due to apoptosis. Apoptosis has been observed in some leukaemia cell lines including HL60 in response to challenge with ATLs. (Diomede. L. Piovani. B. Principe. P. et. al. The induction of apoptosis is a common feature of the cytotoxic action of ether linked glycerophospholipids in human leukaemia cells. Int. J. Cancer. 1994; 57. 645-649).

At high concentrations, the detergent properties of the ATLs begin to induce direct lytic membrane damage. At these high concentrations the toxicity differential between ATLs and naturally occurring ether lipids is progressively eroded, with all types of lipid killing cells by rapid membrane lysis. (Lohmeyer. M. Workman. P. Growth arrest versus direct cytotoxicity and the importance of molecular structure for the in vitro anti-tumour activity of ether lipids. Brit. J. Cancer. 1995; 72: 277 - 286).

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The accumulation of ether - linked lipids in tumour cells is one of the more common changes in the lipid composition of these cells (Falleni. A. Arcangelli. A. Ruggieri. S. Characteristics of ether - linked glycerophospholipids in Friend erythroleukemia cells differentiated by dimethyl sulphoxide or hexamethylene bisocetamids and in non inducible clones treated with induces. Biochem. J. 1988; 255: 731-736).
Ether - linked lipids are particular forms of lipids containing at least one alkyl (or alkenyl) hydrocarbon chain instead of an acyl chain.
The study of the biosynthesis or ether - linked lipids has lead to the discovery that these lipids are products of the dihydroacetons - phosphate pathway which is prominent in malignant cells (Hajra. A.K. The role of acyl dihydroacetone phosphate in tumour lipid metabolism. In: R. Wood (editor). Tumour lipids biochemistry and metabolism. pp 183-199. Amer. Oil and Chem. Joc. Champaign. 1973. Composition of ether - linked subclasses of glycerophospholipids in clones with a different metabolic potential isolated from a murine fibrosarcoma line (T3 cells). Int. J. Cancer. 1995; 62: 230-232.)

Ether lipids influence growth rate - (Howard B. V., Morris H. and Bailey M. J. : Ether lipids glycerol phosphate dehydrogenase and growth rate in tumours and culturated cells - Cancer Res. 1972; 32; 1533 - 1538), tumourgenicity. - (Roos D. S. Choppin P. W. : Tumourgenicity of cell lines with altered lipid composition. Proc Nat Acad Sci. (Wash) : 1984; 81; 7622-7626), cellular differentiation (Fallani A., Manergi C., Rugger S. : composition of ether-linked subclasses of glycerophospholipids in clones with a different metabolic potential isolated from a murine fibrosarcoma line (T3 cells). Int. J. Cancer. 1995; 62: 230-232.), Ether lipids have also been found to influence metastatic potential (Calorini L., Fallani A., Tombaccini D. et al.: Lipid characteristics of RVS transformed BAL - B/C 3T3 cell lines with different spontaneous metastatic potential. Lipids 1989; 24; 685 - 690) and drug resistance - (May G. L., Wright C.C., Dyne M., et al.: Plasma membrane lipid composition of vinblastine - sensitive and resistant human leukaemia lymphoblast. Int. J. Cancer 1988; 42; 728 - 733)

One of the explanation of cancerostatic properties of ether lipids assumes that they play a role in stimulation of the immune system. In particular their potency to activate macrophages has been wildly recognised.
Important steps in the cascade for developing cytotoxic effects on tumour cells are the release of nitric oxide radicals (NO) and tumour necrosis factor (TNF). (Zeisig, R. Rudolf. M. Ene. J. Arndt. D. Influence of hexadecylphosphocholine on the release of tumour necrosis factor and nitroxide from peritoneal macrophages in vitro. J. Cancer. Res. Clin. Oncol. 1995; 121: 69-75).

It is possible to additionally stimulate this release by incubation with interferon gamma. (Uhing. R.J. Adams. D.O. Molecular events in the activation of marine macrophages. Agents Actions. 1989; 26: 9-14).

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In search for easily applicable ether lipids recently a new class of water soluble ether lipids analogues has been synthetised and showed remarkable anti-tumour activity. (Chang. J.L. Hong. Nechaev. A. Krisik. A.J. et. al. Nucleoside conjugates. Synthesis and anti-tumour activity of 1-p-D- arabinofuranosylcytosine conjugates of ether lipids with improved water solubility. J. Med. Chem. 1995; 38: 1629-1634).