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Commentary

Lipids and Liposomes for Improving Efficacy of Cancer Chemotherapy

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(A COMMENT ON: KONNO T, MAEDA H, IWAI *et al.* Effect of arterial administration of high-molecular weight anticancer agent SMANCS with lipid lymphographic agent on hepatoma: a preliminary report. *Eur J Cancer Clin Oncol* 1983, **19**, 1053–1065.)

THE PAPER by Konno *et al.* published in the *European Journal of Cancer and Clinical Oncology* provides evidence to show that lipids may have to play a role in the therapy of cancer patients. The authors administered to 44 patients with mostly unresectable hepatoma via the arterial route a conjugate of a synthetic copolymer of styrene maleic acid and neocarzinostatin dispersed in an iodinated fatty acid ester of poppy seed oil (Ethiodol®) commonly used as a contrasting agent for lymphography. The preliminary results indicate that accumulation of the antimitotic drug occurred in the tumor and that significant regression of the tumor size was induced in several patients. Only minimal side-effects were observed.

Very few attempts have been made to use lipids as a vehicle for the parenteral administration of drugs in man. Most of the experiments carried out in animals used lipid preparations known to be toxic in man. It is probable that the high incidence of adverse effects resulting from the intravenous administration of several lipid preparations in man has precluded further investigation of lipids as drug carriers in patients [1]. At the present time, when a well-tolerated lipid emulsion can be given safely for parenteral nutrition, potential antimitotic compounds whose chemical structure indicates hydrophobic properties are not even synthesized because they are considered unsuitable for therapeutic use in man. Although the data published by Konno *et al.* are limited to the intra-arterial route of administration, they may constitute a stimulus for further investigation on the use of plain lipid preparations as drug carriers in patients.

On the other hand, numerous experiments have been performed in animals using antimitotic compounds entrapped in liposomes. These lipid bilayer vesicles form when phospholipids at a temperature higher than their phase transition temperature are in the presence of water. Because of the presence of lipid bilayers and of aqueous compartments, these biodegradable vesicles have the ability to entrap hydrophilic, lipophilic and amphiphilic compounds [2].

Recently entrapment of water-insoluble experimental antimitotic compounds such as Nocodazole® and NSC 251635—a quinazolone derivative—has been performed in liposomes made of phosphatidylcholine, cholesterol and stearylamine. These liposomal preparations had a higher therapeutic efficacy against the L1210 murine leukemia than the free compound administered as a suspension [3, 4]. NSC 251635 entrapped in liposomes could be given by the intravenous route without marked toxicity and had a higher therapeutic efficacy against the intravenous, peritoneal and subcutaneous forms of L1210 leukemia than when given intraperitoneally. Moreover, there is now evidence that the same preparation can be infused in man by the intravenous route with minimal side-effects [Coune, unpublished data]. These data suggest that in the near future new classes of antimitotic compounds characterized by their water-

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insolubility may be added to the drugs commonly used today.

An interesting property of liposomes is their ability to modify the pharmacokinetics and the tissue distribution of the entrapped drug. This has been shown in several experiments performed in animals injected with liposomes containing a hydrophilic or an amphiphilic antimitotic compound [5, 6]. Prolongation of the plasma half-life of the entrapped drug will probably result in a prolonged exposure of malignant cells to the drug and an improved response of the tumor if the entrapped antimitotic drug is phase-specific. Entrapment in liposomes has even resulted in overcoming resistance to methotrexate in a rodent tumor [7], but despite several examples of such a phenomenon *in vitro*, this is not a general rule *in vivo*. Data available at the present time indicate that entrapment of phase-specific drugs may induce an increased toxicity [8]. On the other hand, the therapeutic activity of cell-cycle-specific antimitotic drugs has not been enhanced by entrapment in liposomes because it is probably related to the peak concentration of the drug in the plasma; in some cases the therapeutic activity has even been markedly reduced [9]. However, the toxicity of the entrapped compounds is usually decreased, as shown by the reduced cardiac toxicity of entrapped adriamycin [10]. This property may confer on the liposome an important advantage for clinical use, provided the entrapment of the drug does not result in a significant reduction of its therapeutic efficacy. Such a situation has been reported for a lipophilic alkylating agent that was tested free and entrapped in liposomes against murine PC6 myeloma [11].

Entrapment of drugs in liposomes results in a modified tissue distribution [5]. This may be one of the mechanisms explaining the reduced side-effects reported above. Liposomes are mainly taken up by the liver and the spleen, contrary to what had been assumed several years ago, when the lipid vesicles were considered as potential specific carriers to malignant cells because of their structural analogy to biological membranes [2] and because of the high endocytosis ability of malignant cells [12]. Targeting of liposomes containing antimitotic drugs is still in its infancy, but several methods are now becoming available for investigation: design of temperature-sensitive liposomes able to release the entrapped drug in tumor sites locally treated by hyperthermia, design of pH-sensitive liposomes able to release drugs in tumor areas where the pH is lower than in normal tissues [2], covalent binding to liposomes of monoclonal antibodies directed to specific tumor cells and incorporation in the liposome structure of tumor cell membrane glycolipids or artificial lipid antigens [13]. Immunochemical targeting of liposomes injected by the parenteral route will necessitate the successful passage of the lipid vesicles from the blood capillaries to the different tumor sites. In most organs capillaries are lined by a continuous endothelium that is an obstacle to the migration of liposomes [14]. However, discontinuous capillaries exist in several malignant tumors and are probably permeable to certain types of liposomes, as are the liver sinusoids.

Another potential application of liposomes in cancer therapy is based on their use for macrophage activation. Parenteral injection of liposomes containing a macrophage-activating factor has resulted in activation of alveolar macrophages that were able to induce regression of pulmonary metastases of an experimental melanoma mice [15].

Although expectations about the use of liposomes as a selective drug delivery system have not been fulfilled, data available today suggest that these versatile vesicles have a role to play in different fields of cancer therapy.

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