EDITORIAL

Liposomal Encapsulation: Making Old and New Drugs Do New Tricks

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Poor therapeutic index has limited the administration and therapeutic efficacy of cytotoxic antineoplastic drugs. It is a major pharmacologic problem to deliver cytotoxic agents to the tumor while reducing or eliminating exposure of susceptible normal tissues. Many unique solutions to this problem have been explored over the last decade. One solution is drug encapsulation in synthetic phospholipid vesicles. The liposome—a synthetic membrane of one or many lipid layers (unilamellar or multilamellar)—was described by Bangham and co-workers (1) in 1965. By the 1970s, their idea had spawned great interest, resulting in the formulation of many different types of liposomes for use in pharmaceutical delivery. There are infinite possibilities for alteration of liposomal size, charge, and chemical structure. Such flexibility provides a distinct advantage for formulations tailored to specific pharmacologic goals and presents unique clinical and experimental opportunities.

Theoretically, the liposome solves many problems of antineoplastic drug delivery. Insoluble or poorly soluble drugs can be administered intravenously (2-4). Drugs that have serious, dose-limiting toxic effects on organs can be packaged in liposomes to avoid exposure of those organs. High peak drug concentrations can be reduced by a liposome formulation resulting in slow drug release. The development of liposomal doxorubicin was driven by the desire to reduce its dose-limiting cardiotoxicity (5). Encapsulation of other currently used antineoplastic agents, including vincristine (6) and cisplatin and its analogs (7), also focuses on improving their therapeutic indexes and increasing aqueous solubility.

Liposomes provide two great advantages to the investigator: (1) flexibility in the formulation of the lipid membrane and (2) the opportunity to reformulate old drugs to do new tricks. But these strengths can also be weaknesses. Since the possibilities of liposome formulation are infinite and each formulation involves different clinical pharmacology, it is necessary to perform laborious, time-consuming, and expensive preclinical toxicology and pharmacology trials for each formulation. Much of the last decade has been spent exploring the pharmacodynamics of liposome formulations in animals. Over the past 5 years, however, the pace of clinical investigation has quickened. Liposomal formulations of a new quinazolone derivative (2), amphotericin B (3,4), macrophage-activating factor (8), doxorubicin (9), and cisplatin analogs (10) are in phase I and II clinical trials.

Serious technical problems have impeded the development of liposomes as viable clinical tools for the delivery of cytotoxic antineoplastic agents to tumors. Many liposomal formulations (11,12) are taken up by liver and spleen macrophages and hepatocytes. Subsequently, the contents of the liposome are released in the macrophage, possibly on exposure to lysosomal enzymes. Thus, rather than delivering the encapsulated cytotoxic agent to the tumor target, the liposome delivers the drug to the liver or spleen macrophage, which may inactivate it. Other liposome formulations are unstable in plasma. Until recently, no analytical procedures could distinguish liposomally bound drugs from unbound and protein-bound drugs in plasma or tissue extracts.

The recent work of Gabizon and associates (13-15), including the report in this issue of the journal, represents important progress in overcoming some of these problems. The investigators systematically evaluated the physiologic pharmacology of a series of liposome formulations containing varied molar ratios of solid-phase and fluid phospholipids, gangliosides, and cholesterol. They found that lipids confering a rigid bilayer (distearoyl phosphatidylcholine and hydrogenated soybean phosphatidylcholine) and formulations containing monosialoganglioside enhanced liposome circulation time. Enhanced circulation times correlated with reduced hepatosplenic drug uptake and increased uptake in peripheral tissues including tumors. The Gabizon team has devised analytical methods to distinguish liposomal from nonliposomal drug. In the work reported in this issue of the journal, they have applied these techniques to demonstrate prolonged circulation and clearance of doxorubicin encapsulated in a liposome consisting of hydrogenated phosphatidylcholine, hydrogenated phosphatidylcholine, and cholesterol.

This work and that of Allen and Chonn (16) and Forssen (17) open new areas of investigation and potential clinical application. One may design the liposome to target the reticuloendothelial system. This is the aim for treatment of Leishmania parasites, which replicate in the macrophage (18); for therapy for liver pathogens, e.g., Mycobacterium avium or Candida (3,4,19); and for achievement of immune stimulation, e.g., delivery of muramyl tripeptidemycobacterium avium or Candida (3,4,19); and for achievement of immune stimulation, e.g., delivery of muramyl tripeptide-phosphatidyl ethanolamine (MTP-PE) to macrophages (20). Alternatively, one may blockade the reticuloendothelial system by sequential liposome injections (21) or design a liposome to avoid macrophage uptake, leading to longer systemic circulation time with reduced hepatosplenic uptake and higher tumor tissue uptake (14-17). Attachment of monoclonal antibodies to the liposomal membrane (22) may further improve targeting.

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Although methods of using liposomes to evade or target the liver appear to be established, we must recognize that the results of rodent model studies require confirmation in trials in larger animals. This is particularly true for studies of doxorubicin, because metabolism of this drug in larger animals differs from that in rodents. Furthermore, even though results of the current study by Gabizon and colleagues indicate that most doxorubicin recovered from the plasma is liposomally bound, identification of the fluorescent species recovered remains important.

Technical problems must be solved before liposomes can be routinely administered to patients. First, attention should be given to development of easy, routine, rapid, and reproducible procedures for formulating liposomal drugs. With at least one exception (23), present methods of liposome formulation require procedures for evaporation, temperature-controlled incubation, and in some cases, dialysis. Such procedures are impractical for day-to-day hospital operations.

Second, the variability of drug incorporation into the liposome should be addressed. The dose of free drug administered when the formulation procedures of the Gabizon team (15) are used should be more accurately quantified, and if possible, the amount of free drug given with the liposomally bound drug should be reduced. Administration of unknown or variable quantities of free drug will compromise the reduction in toxicity that may be achieved by the liposomal formulations.

Focusing on liposomal drug encapsulation as a method of improving tumor drug delivery is only a limited application of the potential of this drug delivery technique. Other promising applications are being explored. Reduction of rapid deamination by encapsulating cytarabine or a derivative that requires enzymatic activation could enhance the therapeutic efficacy of this important antileukemic drug (24). Liposomes alone have immunoadjuvant properties (25) that can be exploited by use as immunostimulants or as carriers for antigens relevant to human and veterinary immunization.

Empty liposomes with a radioactive label (67Ga or 111In) may find uses as tumor-imaging agents (26,27). Exploitation of liposomal uptake by macrophages or hepatocytes has potential for delivery of immunostimulators or antibiotics in the treatment of infectious diseases, particularly those associated with severe immunosuppression, such as leukemias, lymphomas, and acquired immunodeficiency syndrome.

Recent information regarding cell–liposome interactions is provocative and worthy of further investigations. Liposomal formulations may reverse resistance in cell lines (28,29), and fusion of the lipid vesicle with cells may bypass membrane transport barriers. These observations coupled with evidence of immunogenicity suggest the possibility of liposomal modulation of cell membrane functions. Liposome vesicles could be formulated to exploit interaction with important cell membrane receptors such as growth factor or hormone receptors. Modulation of membrane signal transduction could be exploited by use of liposomes with or without encapsulated drugs.

Liposomal drug delivery systems have great potential for many purposes. Future clinical use is likely, provided that the formulation can be reproduced in hospital pharmacies with a minimum investment in personnel, time, and equipment. Solutions to this problem will open new areas of research with the potential to make old drugs do important new tricks, enhance their therapeutic indexes, allow formulation of previously insoluble drugs for intravenous use, provide new approaches to immunization and immunostimulation, and possibly probe important basic aspects of membrane-drug interactions.

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Carboplatin Substitution for Cisplatin in the Treatment of Ovarian Carcinoma—A Word of Caution

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After cisplatin was identified as the first of an important new class of compounds (organoplatinum compounds) with a broad spectrum of antitumor efficacy, a large number of analogs were developed with the hope that one or more would have equivalent antitumor activity without the two adverse effects that made dose escalation and long-term dosing with cisplatin a problem, i.e., renal tubular damage and peripheral neurotoxicity. Both Bristol-Myers and the National Cancer Institute independently chose carboplatin as one analog for development based on preclinical studies suggesting that it had a spectrum of activity similar to that of cisplatin while not producing nephrotoxicity or neurotoxicity. Bone marrow suppression was the dose-limiting adverse toxic effect of carboplatin.

In 1983 the first report was published (1) demonstrating activity of carboplatin in refractory ovarian cancer. A subsequent phase III trial in Britain comparing carboplatin with cisplatin in previously untreated patients with ovarian cancer demonstrated equivalent response rates and superimposable survival curves (2). Nearly 50% of the patients receiving cisplatin in that study had therapy discontinued because of drug toxicity, whereas only 6% of the patients receiving carboplatin had adverse effects necessitating discontinuation of therapy. Within months of this report, carboplatin was approved in both Canada and Great Britain for both first-line and second-line therapy for ovarian cancer. In early 1989, the Food and Drug Administration (FDA) in the United States approved use of carboplatin for second-line therapy in ovarian carcinoma but withheld approval for first-line therapy.

In this issue of the Journal, further data comparing cisplatin and carboplatin as single agents in ovarian cancer are reported (3). A population of 173 stage III (mostly stage IIIC) and stage IV ovarian cancer patients were randomly assigned to five monthly treatments in the outpatient department with cisplatin (100 mg/m²) or carboplatin (400 mg/m²); probably equivalent doses. Outpatient administration time was 12.5 hours for cisplatin and 0.5 hour for carboplatin. Clinical response rate, complete pathologic response rate, median survival, and progression-free survival were similar for both agents. Toxicity was, as anticipated, significantly dissimilar; hematologic toxicity predominated with carboplatin, and nephrotoxicity and neurotoxicity were more pronounced with cisplatin. The authors described significant carboplatin dose adjustments based on planned escalation and de-escalation in response to hematologic parameters. Conversely, little dose adjustment was necessary with carboplatin because there was no planned escalation and because toxicity requiring dose reduction was marginal (i.e., development of peripheral neuropathy or elevation of serum creatinine).

The authors presented with caution the conclusions that they drew from this well-executed and -analyzed study. We agree with their conclusion that substitution of carboplatin for cisplatin (especially in combination regimens) has the potential for adverse end results, although carboplatin is easier for patients to receive and has very acceptable toxicity. We also agree with our own FDA’s withholding of specific approval for first-line therapy until more mature data for carboplatin combinations are available.

In Britain (4), Italy (5), and Canada, single-agent therapy with cisplatin for advanced ovarian cancer is accepted by