Thermally enhanced liposomal drug delivery

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Background

The purpose of this article is to review the concept of using heat to augment thermally sensitive liposomal drug delivery to tumors. If one loads a water soluble drug into the liposome below the lipid melting temperature, the drug will exhibit very slow release, which is dependent upon the solubility of the drug in lipid (1). A thermally sensitive liposome is designed to take advantage of changes in permeability when lipids melt. The mechanism leading to enhanced content release is thought to be related to opening of pores between plates of solid lipid, during the melting process (1). Details of the material science that leads to enhanced drug release will not be reviewed here; further details can be found in other reports (1–4).

Historical Perspective

Milton Yatvin was the first to use hyperthermia with drug loaded thermally sensitive liposomes to enhance drug delivery to tumors (5, 6), but some of the performance characteristics of this liposome were not optimized. Gaber, et al., examined liposomal accumulation and drug release from a pegylated version of the Yatvin liposome (7). Hyperthermia augmented liposome accumulation and drug release in tumors at 42–45°C, but the liposome did not fully release drug and the drug release kinetics were relatively slow (8) (Fig. 1). The slow release was particularly problematic because a liposome would pass through the vasculature of a tumor well before it released drug. To more efficiently capture released drug within the heated tumor, a liposome with faster drug release was sought.

Drs. Dewhirst and Needham collaborated in the development of a temperature sensitive liposome that releases drug at a lower temperature (phase transition = 41.3°C) (9, 10). Upon reaching its transition temperature, doxorubicin was nearly completely released in less than 20s (10). This formulation resulted in 25–30 and fivefold increase in drug delivery to a heated volume vs. free drug or non-thermally sensitive liposomes containing doxorubicin, respectively (11). Several other liposomal formulations have been reported that also exhibit rapid drug release between 41–42°C (3, 4, 12, 13). The acronym "LTSL," which stands for "low-temperature sensitive liposome" is a generic term for this type of formulation.

Drug Delivery Characteristics of LTSL and Clinical Implications

Manzoor and Lindner, et al., used skin-fold window chambers to prove that drug delivery with LTSLs was purely the result of intravascular drug release in the heated tissue (14) (Fig. 2). Thermally mediated drug delivery to a local tumor has advantages and disadvantages, however. For example, it is difficult to justify giving neoadjuvant doxorubicin-LTSL to a woman with
locally advanced breast cancer, because such patients are at high risk for having micrometastatic disease. Viglianti, et al., tested whether doxorubicin-LTSL had systemic effects by performing experiments with mice that had two flank tumors: one was heated and the other was not. Antitumor effects were observed in both tumors (15). These results lend credence to the concept of using doxorubicin-LTSL with hyperthermia to a primary tumor, as some level of systemic antitumor effect is expected.

**Antitumor Effects of Drug Containing LTSL and Practical Limitations**

**Doxorubicin**

Doxorubicin is the most commonly studied chemotherapeutic drug evaluated with the LTSL formulations. Doxorubicin-LTSL + hyperthermia has been tested in a range of different tumor types, including xenografts for head and neck cancer, ovarian cancer, colorectal cancer, breast cancer, melanoma and sarcomas. Improvement in growth delay has been observed in most models, compared with heat alone, free drug and non-thermally sensitive liposome formulations (11, 16, 17).

Doxorubicin-LTSL + hyperthermia causes vascular damage and cessation of perfusion; these effects undoubtedly contribute to the overall antitumor efficacy (18). However, the extent of vascular damage varies between tumor types. It has been reported that intertumoral variation in
antitumor effect of doxorubicin-LTSL is influenced by hypoxia and drug concentrations achieved (19) (Fig. 3). Even with the thermal enhancement of intravascular drug release, the total amount of drug delivered to a tumor is limited by the efficiency of its vasculature.

Other drugs encapsulated in LTSL

By the nature of its composition, the best drugs to encapsulate into liposomes are those that are water soluble. There have been reports of antitumor effects of LTSLs loaded with gemcitabine and cisplatin, for example (20, 21).
Real-time Monitoring of Drug Delivery with LTSL

Viglianti, et al., were the first to report on the concept of using MRI to measure drug and contrast agent release from doxorubicin-LTSL (22). Ponce, et al., was able to demonstrate that differences in drug delivery to individual tumors, as measured with MRI, were correlated with tumor growth delay (Fig. 4) (23).

MR contrast agents have been successfully encapsulated into LTSL by several groups (24–26). The groups involved in focused ultrasound have been particularly interested in LTSLs. The ultrasound devices are already used inside MR magnets in order to measure temperatures, which are needed to ascertain margins of thermally ablated zones. Using LTSLs that contain both MR contrast and cytotoxic drug would enable a clinician to use MRI to monitor drug delivery in real time, during application of ultrasound to a target volume. This would enable adjustment of the ultrasound transducers to maximize drug delivery throughout the tumor volume.

Clinical Development of Doxorubicin-LTSL

Commercial development of doxorubicin-LTSL has focused on two diseases: 1) primary liver cancer, and 2) patients with chest wall recurrences of breast cancer. The rationale for choosing these two diseases has been elucidated (27, 28). In single and multidose phase I trials, the primary dose limiting toxicity has been bone marrow. There has been no evidence for cardiotoxicity or hand-foot syndrome (28, 29); the latter is often seen with long circulating non-thermosensitive liposomes. Antitumor activity has been seen in both diseases (28, 29). The patients with chest
wall recurrences had been heavily treated with doxorubicin previously and their tumors were drug resistant. The data hold promise for the potential utility of this type of product for drug resistant cancers.

A phase III trial was conducted for 701 patients with unresectable primary liver cancer. Half of the patients were randomized to receive radiofrequency ablation alone and the other half had doxorubicin-LTSL added. The final statistical analysis of this trial revealed no difference in progression-free survival between the two groups. Simulations of drug delivery with doxorubicin-LTSL predicted that an ablation time >45 min was required to optimize drug delivery to the ablation margin (30). Indeed, in post hoc analysis, patients who received at least 45 min of ablation + doxorubicin-LTSL experienced a significant prolongation of progression-free survival compared with thermal ablation alone. These observations led to the initiation of a second phase III trial (Optima; Protocol IDs: 104-13-302, NCT02112656). The inclusion criteria are more selective for this trial. Patients with multiple lesions are excluded and 45 min of thermal ablation are required.
Discussion

Progress with thermosensitive liposomes has accelerated over the past ten years. In large part, this has been driven by their potential applications with thermal ablation technologies, which include radiofrequency, microwave, lasers, and ultrasound. The technology lends itself to integration with ablative technologies (where temperatures are between 60 and 100°C), although one could envision several applications with traditional hyperthermia, which is delivered at temperatures in the range where LTSLs release drug (39–42°C).

Future Directions

Considerable progress has been made in integrating high intensity focused ultrasound with doxorubicin-LTSL. High intensity focused ultrasound is approved in Europe and/or the US for bone metastases and prostate cancer. Several other clinical applications are possible, including breast cancer and brain tumors. There is increasing interest in using LTSLs that are doubly loaded with drug + MR contrast agent. If successful, it would be possible for the first time, to literally watch drug being deposited in a target volume in real time. This could enable modification of treatment parameters on the fly, to perform "drug dose painting" of the target volume.

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