A Comparative Study of Folate Receptor-Targeted Doxorubicin Delivery Systems: Dosing Regimens and Therapeutic Index

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Abstract
Supramolecular drug delivery nanosystems are designed to accumulate in tumors by extravasation-dependent targeting through the leaky vessels via the enhanced permeability and retention (EPR) effect. The conjugation of targeting moieties results in receptor-mediated drug delivery. Folic acid (FA) is a low molecular weight ligand of the folate receptor (FR), widely used as targeting agent due to overexpression of FR on many tumor types. In this study, we compared the selectivity, safety and activity of doxorubicin (Dox) entrapped in PEGylated liposomes (PLD) versus Dox conjugated to polymeric Pullulan nanocarriers (Pull-Dox), targeted with FA (PLD-FA² and FA-Pull-Dox⁴). Both receptor-targeted nanosystems were shown to interact in vitro specifically with cells via the FA.

Treatment of FR-overexpressing human cervical carcinoma KB tumor-bearing mice with three-weekly injections resulted in enhanced anticancer activity of FR-targeted Dox-loaded PEGylated liposomes (PLD-FA) and Dox-loaded PEGylated liposomes (PLD), with slight advantage for PLD-FA. Under the same regimen, there was no significant reduction of tumor size with both pullulan-based conjugates (Panel A). When the nanosystems were administered intravenously every other day, the FA-Pull-Dox and the Pull-Dox displayed similar and low antitumor activity as compared to free Dox. At this dosing regimen, the liposome-based formulations displayed again enhanced antitumor activity with a slight advantage for PLD (Panel B). However, both liposomal formulations caused toxicity that was reversible following treatment discontinuation. Using a daily dosing schedule, the FA-Pull-Dox conjugate strongly inhibited tumor growth, and was significantly more active than the Pull-Dox conjugate, while free Dox was toxic at this regimen (Panel C). For polymeric constructs, increasing dose intensity and cumulative dose strongly affects the therapeutic index and reveals a major therapeutic advantage for the FR-targeted formulation. Liposome-based nanosystems require longer dose intervals to prevent toxicity. All nanosystems were able to abrogate Dox-induced cardiotoxicity. This study reports the first side-by-side comparison of two receptor-targeted systems, namely polymer therapeutics versus nanoparticulate systems, that were evaluated in the same mouse tumor model at several dosing regimens.

References

Figures

A

B

C

- ▲ Saline
- ▼ PLD
- ▼ PLD-FA
- ▼ (NH₂-PEG)-Pull-(Cyst-Dox)
- ▼ (FA-PEG)-Pull-(Cyst-Dox)

- ▲ Saline
- ▼ Dox
- ▼ PLD
- ▼ (NH₂-PEG)-Pull-(Cyst-Dox)
- ▼ (FA-PEG)-Pull-(Cyst-Dox)