Enhanced Exposure of a Chemotherapeutic Drug to the Lymphatic System with the use of PEG-Modified and Nano-Sized Drug Carriers

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ABSTRACT SUMMARY

The lymphatic system is a major pathway by which metastasizing cancers spread throughout the body. Metastasizing cancers that arrest within lymph nodes are also able to seed further tumours to distal locations. Targeting chemotherapeutic agents towards the lymphatic system offers an approach to improve the treatment of lymph-metastatic cancers and to potentially limit systemic side effects commonly associated with chemotherapy. The current study therefore assessed the ability of different nano-sized, polyethylene glycol (PEG) modified drug carriers to enhance the exposure of the anti-cancer drug doxorubicin to the lymphatic system in rats after intravenous or subcutaneous administration. A dendrimer-based formulation of doxorubicin significantly improved the lymphatic access of the drug when compared to the administration of a solution formulation and a liposomal formulation of doxorubicin. The work demonstrates the potential for dendrimer-based drug delivery systems to improve the exposure of lymph-resident metastases to chemotherapeutic drugs.

INTRODUCTION

Cancers which spread via the lymphatic system often arrest within lymph nodes and develop into metastatic legions which can then seed further tumours at distal locations (1). The surgical removal of sentinel lymph nodes is frequently employed to limit metastasis, but this is often ineffective. Also, while the intravenous delivery of small molecule chemotherapy drugs may be effective against the primary tumour, these typically do not effectively access the lymph.

EXPERIMENTAL METHODS

The lymphatic pharmacokinetics of a solution formulation of doxorubicin, a PEGylated liposome formulation of doxorubicin and a PEGylated polylysine dendrimer-based formulation of doxorubicin (4) were compared in thoracic lymph duct cannulated male Sprague Dawley rats (2). Rats were dosed either IV via a jugular vein cannula or SC into the left hind heel and blood and lymph samples were collected for 30 h in lymph cannulated rats, and for up to 7 days in non-lymph cannulated control rats. At the end of the study, iliac, inguinal and popliteal lymph nodes were collected. Samples were analysed for doxorubicin concentration via a validated HPLC method with post-column fluorescence detection.

RESULTS AND DISCUSSION

The lymphatic delivery of chemotherapeutic drugs can be improved, however, via formulation into nanosized drug carriers. For instance, previous work has shown that PEGylated liposomes (~100 nm) and dendrimers (~10-13 nm) are absorbed to some extent from subcutaneous injection sites via the lymph (2, 3). To this point, however, the relative efficiency of dendrimer-based and liposomal delivery systems in enhancing the lymphatic exposure of drugs has not been examined.

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Liposomal and dendritic formulations of doxorubicin significantly increased the lymphatic recovery of doxorubicin by ~190 fold and ~720 fold respectively after SC dosing (Figure 1).
Interestingly, IV administration of the dendritic formulation also significantly improved lymphatic exposure to doxorubicin when compared to IV administration of the solution formulation (by 290 fold). The dendritic formulation also enhanced the recovery of doxorubicin within lymph nodes draining the SC injection site by up to 15-fold when compared to liposomal and solution formulations of doxorubicin (Figure 2).

The increase in lymphatic and lymph node exposure upon IV or SC administration of the dendrimer-based formulation when compared to the liposomal or solution formulation may be attributed to more efficient removal of the smaller dendritic system from the injection site, and by the efficient reuptake of extravasated dendrimer via the lymphatics across capillary beds.

CONCLUSION
This study demonstrated the ability of nano-sized, PEGylated drug vectors to greatly enhance the exposure of doxorubicin to the lymphatic system following both IV and SC administration. In particular, the ability of the small dendritic construct to deliver larger quantities of doxorubicin to the lymphatics when compared with liposomal or solution based formulations suggest that lymphotropic dendrimer-based drug delivery systems may provide a promising new treatment for lymph metastatic cancers.

REFERENCES

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