Lauroyl-gemcitabine loaded lipid nanocapsules for the treatment of metastases in mediastinal lymph nodes
Nathalie Wauthoz, Elodie Moysan, Kazuya Kondo, Marc Zandecki, Valérie Moal, Marie-Christine Rousselet, José Hureaux, Guillaume Bastiat, Jean-Pierre Benoit

To cite this version:
Nathalie Wauthoz, Elodie Moysan, Kazuya Kondo, Marc Zandecki, Valérie Moal, et al.. Lauroyl-gemcitabine loaded lipid nanocapsules for the treatment of metastases in mediastinal lymph nodes. 9th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Mar 2014, Lisbon, Portugal. 2014. hal-03173099

HAL Id: hal-03173099
https://univ-angers.hal.science/hal-03173099
Submitted on 18 Mar 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
Lauroyl-gemcitabine loaded lipid nanocapsules for the treatment of metastases in mediastinal lymph nodes.

N. Wauthoz1, E. Moysan1, K. Kondo2, M. Zandecki3, V. Moal3, M.-C. Rousset3, J. Hureaux1,2, G. Bastiati, J.-P. Benoit1

1 LUNAM Université – Micro et Nanomédecines Biomimétiques, INSERM – U1066 IBIS-CHU, F-49933, Angers, France, email: guillaume.bastiati@univ-angers.fr
2 Department of Oncological Medical Services, Institute of Health Biosciences, The University of Tokushima, Tokushima 770-8503, Japan
3 Hematology, Biochemistry, Cell and Tissue Pathology and Pneumology Departments, Academic Hospital, Angers, F-49933, France.

INTRODUCTION
Tumour cells may cause the leaching of cancer-related mortality around the world (SIEGEL et al, CA Cancer J. Clin., 2013). Once diagnosed, non-small cell lung cancers (NSCLC)’s 5-year survival rate reaches globally 15% with the different therapeutic modalities such as surgery, radiotherapy and chemotherapy. For most patients, NSCLC has spread in mediastinal and subcarinal lymph nodes (N2 disease, stage III) or in the contralateral lung, pleural cavity or beyond lung (M1 disease, stage IV) (RUNG et al, J. Clinonc., 2012). In aim to protect the drug until the site of action, target the lymph nodes invaded by metastases and decrease the related systemic toxicities, nanomedicine could be a very great tool (SCHROEDER et al, Nat. Rev. Cancer, 2012).

Lipid nanoparticles (LNC) loaded with a lauroyl-modified gemcitabine (Gem-C12) have been developed and demonstrated the ability to form a hydrogel by nanoparticle assembly (MOYSAN et al, Soft Matter, 2013). These nanocarriers could be delivered as a gel by subcutaneous (sc) route or as a suspension (after dilution) for intravenous (iv) administration. The purpose of this study is to reach passively the lymph nodes in vivo, and to evaluate the antitumour efficacy of this new system in a human NSCLC metastatic model, which mimics the spreading of metastases in mediastinum from the primary tumour implanted in the lung of mice. The tolerance (myelo-suppression and hepatotoxicity) of this new treatment delivered either as a gel by sc route or as a suspension by iv route was also investigated.

LAUROYL-MODIFIED GEMCITABINE–LOADED LIPID NANOCAPSULES

A single dose of Gem-C12-trapped LNC in suspension (sc injection iv dose) was used to obtain the intranodal LNC association.

IN VIVO BIODISTRIBUTION IN HEALTHY AND TUMOR-BEARING MICE

An immediate accumulation in liver and spleen, and in all lymph nodes was observed with DD-loaded LNC suspension intravenously delivered. DDGEM-C12-trapped LNC in gel form substantially delivered accumulated exclusively in the lymph nodes close to the injection site and presented a very low systemic exposition.

With tumor-bearing SCID-CB17 mice, DD-LNC were visible in the entire lung of the three mice after iv injection. On the contrary, DD-LNC administered by sc route emitted an intense local accumulation in mediastinal/lung lymph nodes in the pictures.

IN VIVO ANTI-TUMOR EFFICACY AND TOLERANCE OF TREATMENTS

The Kaplan-Meier survival curves and the weight evolution of mice (n=10 per group) grafted with NCI-H522 cells after various gemcitabine treatments (total dose of 40 mg/kg, molecular equivalent gemcitabine hydrochloride).

Significant level (p < 0.05, log-rank test) was reached with all gemcitabine treatments in comparison to controls (treatment without drug). However, there was no significant difference between the survival rates of groups treated by gemcitabine regardless of the route of administration. The weight evolution of the different groups mice remained similar during the treatment period.

Treatment with non-encapsulated Gemcitabine presented significant decreases (p < 0.05, Kruskal-Wallis test) of platelet count and alkaline phosphatase. No difference was measured for plasma biochemical parameters and complete blood counts when Gem-C12 was encapsulated inside LNCs, regardless of the route of administration.

CONCLUSION

The lipid nanocapsules loaded with a lipophilic derivative of gemcitabine were able to target the lymph nodes and more specifically the mediastinal lymph nodes, displaying a similar antitumor efficacy as the conventional systemic gemcitabine in the lymphomagenic metastatic preclinical model with a treatment schedule of twice a week iv in comparison to three times a week iv for the standard drug. Moreover, LNC loaded with Gem-C12 and delivered iv or sc did not induce myelo-suppression unlike the conventional systemic gemcitabine. This latter feature shows clearly the advantage brought by a nanostructured formulation of gemcitabine.

ACKNOWLEDGMENTS
This work has been realized within the research program ‘LYMPHOTARG’ financially supported by EuroNanoMed ERA-NET 09 and by the Region Pays de la Loire.