British Journal of Pharmacy

https://doi.org/10.5920/bjpharm.1173

British Journal of Pharmacy

www.bjpharm.hud.ac.uk

Proceedings of the 13th APS International PharmSci 2022

Histopathological impact of Redox-responsive methacrylamide based micellar nanoparticles on Orthotopic Models of Triple Negative Breast Cancers

Fatemeh Mehradnia[a], Cara Moloney[b], Robert J Cavanagh[b], Amanda K Pearce[a], Alison Ritchie[a], Philip Clarke, Ruman Rahman[a], Asmaa Ibrahim[b], Anna M. Grabowska[b] and Cameron Alexander[a,*]

[a]School of Pharmacy, University of Nottingham, Nottingham, NG7 2RD, UK

[b]School of Medicine, University of Nottingham, Nottingham, NG7 2RD, UK

ARTICLE INFO

Received: 16/06/2022
Accepted: 07/07/2022
Published: 03/11/2022

*Corresponding author.
E-mail:
Cameron.alexander@nottingham.ac.uk

KEYWORDS:

Redox-responsive micellar nanoparticles;Histopathology; apoptosis; Triple negative breast cancer.

SUMMARY

The therapeutic efficacy of anticancer nanocarriers is highly dependent on their size, shape, targeting ability, and stimuli-responsiveness. Herein, we studied the *in vivo* therapeutic efficacy of Doxorubicin (Dox) loaded redox responsive micellar-like nanoparticles (MNPs) based on linear 2-hydroxypropyl methacrylamide (HPMA) via histopathological evaluations. The nanoparticles improved the therapeutic efficacy of DOX while significantly reduced cardiotoxicity and hepatotoxicity. H&E staining of tumor tissues indicated the higher population of apoptotic tumor cells in Dox-MNP treatment group. These redox responsive crosslinked HPMA-based MNPs with acceptable therapeutic efficacy and apoptosis induction in cancerous cells proved to be promising nanomedicine for breast cancer chemotherapy.

INTRODUCTION

Nanotherapeutics with optimized formulations have shown enhanced antitumor efficacy and reduced side effects due to higher accumulation in tumor tissue and lower accumulation in normal tissues owing to the permeation and retention (EPR) effect [Rehman et al., 2020; Moradi et al., 2021]. Stimuli-responsive nanocarriers that show enhanced blood circulation time and triggered drug release at target sites in response to a specific stimulus are promising candidates as efficient cancer nanomedicine. Cross-linking by reversible linkers has emerged as an ideal approach for improving the blood circulation stability of nanocarriers. Disulfide cross-linked polymeric micellar nanocarriers trigger release of drug from in the intracellular space due to the markedly high glutathione (GSH) concentration in tumor environments of [Mollazadeh, Mackiewicz, & Yazdimamaghani, 2021]. The aim of this study was to examine the anticancer therapeutic efficacy of previously developed redox responsive micellar-like nanoparticles based on linear 2-hydroxypropyl methacrylamide (HPMA) [Pearce et al., 2020] and their cardiotoxicity and hepatotoxicity in tripe negative breast cancer (TNBC) bearing mice via histopathological analysis.

MATERIALS AND METHODS

The animals from different experimental group, control, free Dox and Dox-MNPs were sacrifized 46 days post-treatment, and the harvested tissues including tumor, heart and liver were fixed in 10%

https://doi.org/10.5920/bjpharm.1173

formalin (pH. 7.26) for 48 h. Formalin-fixed paraffin-embedded tissue blocks were sectioned by microtome to obtain 10-µm thick tissue sections and then mounted on pre-treated glass slides. For haematoxylin and eosin (H&E) staining, the tissue sections were first de-paraffinised in xylene. In the next step, the sections were re-hydrated in decreasing grades of alcohol followed by washing with deionized water. The slides were then stained with H&E, followed by dehydration in increasing amount of grades of alcohol and xylene. The slides were then mounted using a xylene based premount and covered with cover slips for observation by bright field microscopy (Olympus, Japan) microscopy at 40 × magnification.

RESULTS AND DISCUSSION

The H&E-stained tissue sections from all experimental groups were examined histologically. The heart and liver sections in the control and Dox-MNPs groups had a normal architecture however some degeneration and disorganization of the liver cells was observed in Dox-MNPs sections. The normal structure of the liver was somewhat lost in Free-Dox section. Tumor sections in Dox-MNPs group showed extensive apoptosis and necrosis associated with moderate to marked inflammatory cell infiltrate together seen with scattered apoptotic bodies, which was not the case in control and Free Dox group. Dox encapsulation in micelles improves its tumor accumulation and simultaneously decreases its accumulation in the healthy tissues and enriched drug into the tumors which consequently results in enhanced apoptosis and therapeutic efficacy and less toxic side effects

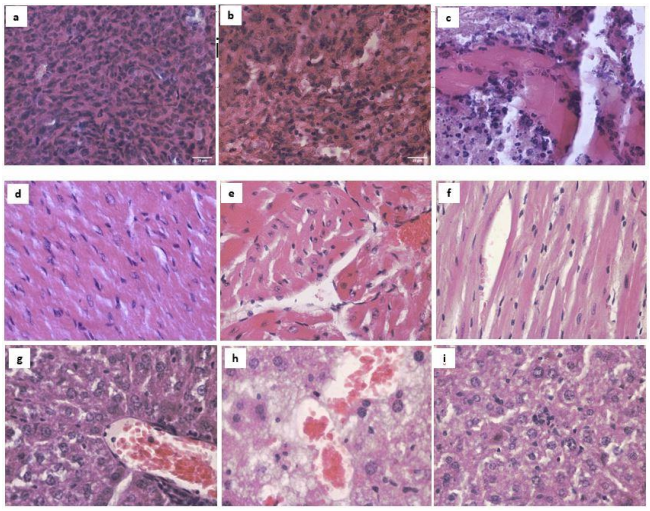

Fig. 1. *H&E staining of TNBC tumor, heart and liver tissues in different groups 46 days post treatment. Tumor in a) control, b) Free Dox, c) Dox-MNPs groups; Heart in d) control, e) Free Dox, f) Dox-MNPs groups; Liver in g) control, h) Free Dox, i) Dox-MNPs groups. (40x magnification*

CONCLUSIONS

The enhanced apoptosis induction in cancerous cells and reduced cardiotoxicity and liver toxicity of redox-responsive HPMA-based micellar-like nanoparticles indicated the promising potential of this nanotherapeutic for breast cancer therapy. However, it is suggested to target the MNPs to improve their therapeutic efficacy.

REFERENCES

Mollazadeh, S., Mackiewicz, M. and Yazdimamaghani, M., 2021. Recent advances in the redox-responsive drug delivery nanoplatforms: A chemical structure and physical property perspective. Materials Science and Engineering: C, 118, p.111536.

Moradi, H., Beh Aein, R. and Youssef, G., 2021. Multi-objective design optimization of dental implant geometrical parameters. International Journal for Numerical Methods in Biomedical Engineering, 37(9), p.e3511.

Rehman, A., Jafari, S.M., Tong, Q., Riaz, T., Assadpour, E., Aadil, R.M., Niazi, S., Khan, I.M., Shehzad, Q., Ali, A. and Khan, S., 2020. Drug nanodelivery systems based on natural polysaccharides against different diseases. Advances in Colloid and Interface Science, 284, p.102251.

Pearce, A.K., Anane-Adjei, A.B., Cavanagh, R.J., Monteiro, P.F., Bennett, T.M., Taresco, V., Clarke, P.A., Ritchie, A.A., Alexander, M.R., Grabowska, A.M. and Alexander, C., 2020. Effects of polymer 3D architecture, size, and chemistry on biological transport and drug delivery in vitro and in orthotopic triple negative breast cancer models. Advanced Healthcare Materials, 9(22), p.2000892.