

Considerable Anti-Tumour Effect of Nanoparticle-Bound Doxorubicin against 4T1 Metastatic Breast Cancer in Mice

Yulia Malinovskaya¹, Svetlana Gelperina¹, Olga Maksimenko¹, Vladimir Baklaushev²

¹R-Pharm Drugs Technology Ltd.

Khimki, Moscow Region, 141400, Russia

²Serbsky State Scientific Center for Social and Forensic Psychiatry

Moscow, 117418, Russia

j.malinovskaya@gmail.com

Extended Abstract

Introduction: Our previous results demonstrated a considerable antitumor effect of doxorubicin loaded in PLGA nanoparticles (Dox-PLGA NPs) coated with poloxamer 188 (P188) against the intracranial 101.8 glioblastoma in rats [1,2]. As a high-grade breast cancer is a common cause of brain metastases occurring in at least 10-16% patients [3] and doxorubicin is widely used against breast cancer, the aim of the present study was to evaluate the efficiency of Dox-PLGA NPs against 4T1 metastatic breast cancer in Balb/c mice.

Methods: Dox-PLGA NPs were prepared by a double emulsion solvent evaporation technique. *Chemotherapy:* 4T1 murine breast cancer cells were previously modified by firefly luciferase gene transfection (4T1-Luc2) and inoculated intracardially (1×10^5) into the cavity of a left ventricle of female Balb/c mice. On days 7, 10, 13, 16, and 19 after intracardial injection the tumor-bearing animals received i.v. the following formulations in the dose of 2 mg/kg (as doxorubicin): 1) Doxorubicin solution (Dox-sol), 2) Dox-PLGA NPs in PBS (DOX-PLGA), 3) Dox-PLGA NPs coated with 1% poloxamer 188 (Dox-PLGA/P188). For coating the NPs were resuspended in 1% P188 30 min before injection. Animals treated with 1% P188 solution and untreated group were used as controls 1 and 2, respectively. Organ bioluminescence intensity was assessed using an intravital fluorescence imaging system Ivis Spectrum CT on days 14 and 28 after tumor inoculation. Additionally, the presence of metastases in surviving animals was confirmed by MRI on days 21 and 28.

Results: The average particle diameter was 120-130 nm, and the drug loading was 84%. The mean survival time of tumour-bearing mice was increased by >40% after treatment with Dox-PLGA NPs, as compared to control (23 days versus 15-16 days, respectively). As shown by intravital fluorescence imaging, the improved survival in the nanoparticle-treated groups also correlated with significantly lower fluorescence intensity of metastases as compared to the group treated with Dox-sol and control groups. The difference between the groups treated with DOX-PLGA and Dox-PLGA/P188 was not significant; however, in the animals treated with P188-coated NPs a somewhat lower bioluminescence of metastases was observed. Importantly, administration of nanoparticulate formulations was associated with a significantly improved tolerance of chemotherapy, as compared to free doxorubicin.

Conclusion: Binding of doxorubicin to PLGA nanoparticles considerably enhanced its antitumour efficacy against 4T1 metastatic breast cancer in mice providing more pronounced inhibition of metastatic spread and higher increase of animal life-span, as compared to the free drug. Moreover, Dox-PLGA NPs appeared to be less toxic which is most probably due their altered biodistribution pattern.

References

- [1] S. Gelperina, et al., "Drug delivery to the brain using surfactant-coated PLGA nanoparticles. Influence of the formulation parameters," *Eur J Pharm Biopharm*, vol. 74, pp. 157-163, 2010.
- [2] S. Wohlfart et al., "Efficient chemotherapy of rat glioblastoma using doxorubicin-loaded PLGA nanoparticles with different stabilizers," *PLoS One.*, vol. 6, no. 5, e19121, 2011.
- [3] N. U. Lin, et al., "CNS Metastases in Breast Cancer," *J Clin Oncol*, vol. 22, pp. 3608-3617, 2004.