

Metronomic Nanocaged Doxorubicin Prevents Chemoresistance and Cardiotoxicity in Breast Cancer

Serena Mazzucchelli¹, Marta Truffi¹, Michela Bellini³, Maria A. Rizzuto³, Davide Prosperi³, Fabio Corsi^{1,2}

¹Department of Biomedical and Clinical Sciences, University of Milan

Via G. B. Grassi 74, 20157 Milan, Italy

serena.mazzucchelli@gmail.com; marta.truffi@unimi.it

²Surgery Department, Breast Unit, ICS Maugeri S. p. A. SB

Pavia, Italy

fabio.corsi@unimi.it

³Department of Biotechnology and Biosciences, University of Milan- Bicocca

Piazza della Scienza 2, 20126 Milan, Italy

michi.bellini@gmail.com; m.rizzuto3@campus.unimib.it; davide.prosperi@unimib.it

Extended Abstract

Low-dose metronomic (LDM) chemotherapy is based on frequent administration of a lower dose of drugs, without the need of extensive interruptions [1]. LDM affects the vasculature growth and repair [1] and stimulates the host immune system against the tumor [2], while it has not activity against tumor cells. Nanotechnology could improve the effectiveness of LDM chemotherapy, by taking advantage of the unique targeting efficiency of engineered nanocarriers [3].

In the present work, we propose a new concept of low dose “nanometronomic” (LDNM) chemotherapy, using doxorubicin (DOX) as pilot drug. As an ideal DOX nanocarrier, we used H-Ferritin (HF_n) nanocages, owing to its affinity for transferrin receptor 1 (TfR-1), which is constitutively overexpressed in cancer cells [4]. HF_n-DOX complex was recently demonstrated to overcome chemoresistance by actively promoting DOX nuclear translocation in vitro [4].

4T1-L tumor bearing mice were treated with placebo, DOX, liposomal-DOX (pl-DOX) or HF_n-DOX under our LDNM setting. The progression of tumor volume was monitored in vivo demonstrating that HF_n-DOX could decrease tumor growth, while DOX displayed a tumor progression similar to the control. An even better effect was achieved with pl-DOX, which was indeed able to arrest the tumor development. Moreover, we find that HF_n-DOX antitumor effect is attributable to multiple nanodrug actions beyond cell killing, including inhibition of tumor angiogenesis and avoidance of chemoresistance. Otherwise, although an even better reduction of tumor progression was achieved with pl-DOX a fivefold increase in MDR1 positive cells has been displayed, suggesting that liposomal DOX is not suitable in view of a protracted metronomic treatment, due to the onset of chemoresistance. [5]. Multiparametric assessment of heart tissues, has been performed to investigate the cardiotoxicity of the metronomic HF_n-DOX treatment [6]. Histological evaluations of cardiomyocyte cross-sections from mice treated with HF_n-DOX, pl-DOX, DOX or non-treated was coupled with ultrastructural assessment of morphological alterations in mitochondria number, surface area and cristae depletion. Pathological alterations were detected in DOX and pl-DOX samples suggesting a strong cellular damage response compared to HF_n-DOX samples. Therefore, the absence of obvious alterations in heart samples from mice treated with HF_n-DOX strongly supports the lack of cardiotoxicity in LDNM HF_n-DOX treatment, even compared to pl-DOX, which is currently considered the most safe anthracycline therapy in terms of cardiotoxicity. DOX and pl-DOX ultrastructural cardiac alterations were also associated to functional ones, such as the decrease in mitochondrial membrane potential and the reduction in the reactive oxygen species (ROS) quencher, GSH, confirming mitochondrial dysfunction induced by treatment with DOX and pl-DOX only.

In summary, this study provides robust evidence that LDNM monotherapy with HF_n-DOX is expected to remodel the therapeutic outcome of advanced metastatic BC compared to the drug alone and also to improve anthracycline therapies based on liposomal DOX, with a redefinition of the central role of DOX for solid malignancies under the new perspective of metronomic treatments.

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