Abstract P6-12-17: H-ferritin allows nanometronomic treatment of breast cancer with doxorubicin preventing drug resistance and circumventing cardiotoxicity

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Abstract

Chemotherapeutic treatment of breast cancer is based on maximum tolerated dose (MTD) approach.[1] However, advanced stage tumors are not effectively eradicated by MTD owing to suboptimal drug targeting, onset of therapeutic resistance and neoangiogenesis. In contrast, “metronomic” chemotherapy is based on frequent drug administrations at lower doses, resulting in neovascularization inhibition and induction of tumor dormancy.[1,2] However, several limiting factors remain for LDM in order to displace MTD treatments in clinical practice, including 1) low drug accumulation at tumor site,[2] 2) controversial effectiveness against chemoresistance in advanced metastatic cancers, and 3) acquired resistance after prolonged treatment. Recent advances in nanotechnology could offer groundbreaking solutions to improve the effectiveness of LDM chemotherapy, by taking advantage of the unique targeting efficiency of engineered nanocarriers.[3]Here, we propose a new concept of “nanometronomic” chemotherapy, exploiting the H-ferritin (HFn)-mediated targeted delivery of doxorubicin (DOX)in an aggressive and metastatic breast cancer mouse model with DOX-inducible chemoresistance. HFn nanocages naturally target cancer cells[4] owing to its affinity for transferrin receptor 1. HFn-DOX was recently demonstrated to overcome chemoresistance by actively promoting DOX nuclear translocation in vitro[5,6] and was tested as a MTD treatment on a DOX-sensitive tumor model with encouraging results.[7] We find that LDM administration of HFn-DOX strongly improves the antitumor potential of DOX chemotherapy arresting the tumor progression. Indeed, in vitro and in vivo results demonstrate that HFn nanocages mediate the nuclear delivery of DOX and increase DOX accumulation both in tumor tissue and in cancer cell nuclei, resulting in increased efficacy. Moreover, we find that HFn-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 liposomal DOX (pl-DOX) a five-fold increase in MDR-1-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. Multiparametric assessment of heart tissues, including histology, ultrastructural

analysis of tissue morphology, and measurement of markers of reactive oxygen species and hepatic/renal conditions, provided evidence that metronomic HFn-DOX allowed us to overcome cardiotoxicity contrary to what is observed with DOX and pl-DOX. Our results suggest that HFn-DOX has tremendous potential for the development of “nanometronomic” chemotherapy toward safe and tailored oncological treatments.

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