Differential anti-tumor and cardiovascular effects of Trastuzumab and T-DM1 in a xenotransplant model of NSCLC

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The understanding of the molecular mechanisms underlying tumorigenesis has led to the introduction of so-called targeted therapies, or therapy tailored to tackle on specific tumors according to their molecular characteristics. However, one of the emerging problems of anti-cancer strategies, including new molecularly targeted drugs, resides in the incidence of adverse cardiovascular effects.

Trastuzumab (TSZ) is a potent anticancer monoclonal antibody against HER2, a human epidermal growth factor receptor. Trastuzumab emtansine (a microtubule polymerization inhibitor, T-DM1) is a novel HER2 directed antibody–drug conjugate which is effective against several cancers and able to overcome TSZ resistance. The potency of these innovative approaches may be associated with an increased incidence of side effects involving the cardiovascular system. Importantly, little is known about the mechanisms involved in this phenomenon and experimental observations aimed at the combined investigation of the anti-tumor effect with the potential cardiotoxicity are severely limited.

The aim of the present study was to test whether TSZ and T-DM1 activity is conditioned by HER2 expression in NSCLC and if HER2 targeting tyrosine kinase inhibitors induce cardiac abnormalities.

To this purpose we compared the in vivo effect of TSZ and T-DM1 in a model of small and large NSCLC xenografts.

Tumor xenografts were generated by subcutaneous injection of Calu-3 (human adenocarcinoma cell line) in immunosuppressed BALB/c nude mice. Animals carrying stable xenograft tumors were randomized in three groups to receive once a week: saline solution 1ml/kg (Control); TSZ- 15 mg/kg or T-DM1- 15mg/kg. At sacrifice, tumor nodules and hearts were excised and processed for the subsequent morphological and immunohistochemical analysis. In addition, a small fragment of each tumor xenograft was enzymatically digested to isolate and expand cancer cells in vitro. Xenograft ccomposition was evaluated on sections stained with Masson's trichrome in order to assess the volume fraction of neoplastic tissue, connective tissue and vascular interstitium.

Moreover, the effects of the pharmacological treatment on neoplastic cells proliferation and HER-2 expression was evaluated by immunohistochemistry.

The presence of cardiotoxic effects was determined by the assessment of myocardial fibrosis and cardiomyocyte apoptosis was assessed by the TUNEL assay. Arterioles distribution was measured by a-smooth muscle actin (α-sma) immunostaining.

Results indicated that although TDM-1 was superior to TSZ, treatment with both drugs of HER2 overexpressing tumors was effective in reducing cancer growth by acting selectively on neoplastic epithelial cells without affecting the tumor interstitium. In agreement with recent studies, we observed a greater expression of HER2 on small tumors compared to large ones. Thus, the increased HER2 expression on the cell surface of cancer cells resulted in a greater response to targeted therapy.

Both drugs increased myocardial fibrosis and induced cardiomyocyte apoptosis. However, in the presence of a superior anti-tumor activity, T-DM1 treatment was associated with increased myocardial damage compared to TSZ.

The biologic characteristics of neoplastic cells isolated from treated and untreated xenografts is under extensive investigation to assess whether HER-2 inhibition may induce irreversible changes or clonal selection on its target cell population.

The identification of specific factors implicated in adverse cardiovascular effects by different anti-cancer agents is essential to find effective strategies able to prevent cardiotoxicity without affecting antitumor activity.