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Original research article

Spironolactone ameliorates the cardiovascular toxicity induced by concomitant trastuzumab and thoracic radiotherapy

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ABSTRACT

Aim: We aimed to evaluate impact of spironolactone (S) on cardiovascular toxicity of concomitant use of radiotherapy (RT) and trastuzumab (T).

Background: S, an aldosterone receptor antagonist, is known to ameliorate the cardiac damage. S ameliorates anthracycline -induced cardiotoxicity, there is no data regarding to effect of S on both T and radiation-induced cardiotoxicity.

Materials/Methods: Eighty rats were divided into eight groups: group (G) 1 was defined as control group. G2, G3 and G4 were RT, S and T groups respectively. G5, G6, G7 and G8 were RT + T, T + S, RT + S and RT + T + S groups respectively. Rats were sacrificed at 6th hour; 21st and 100th days after RT. Heart and thoracic aorta samples were taken for microscopical examination.

Results: Cardiac inflammation and fibrosis scores and; TGF-β expression were not significantly different within study groups at 6th hour and 21st days of RT. By 100th days of RT fibrosis scores and TGF-β expression in cardiac samples were significantly different between study groups (p values were 0.004 and 0.002 respectively). Pair-wise comparisons revealed that both cardiac fibrosis scores and TGF-β expression levels were higher in G5 when compared to G8 (p values were 0.046 and 0.028 respectively). Moreover the TGF-β expression was higher in G5 when compared to G2 ($p = 0.046$). We could not demonstrate any significant differences with respect to inflammation, fibrosis and TGF-β expression in thoracic aorta samples between study groups.

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Conclusions: Although S had a protective effect on cardiac tissue it had no protective effect on thoracic aorta when administered with RT + T.

1. Background

Fifteen percent to 25% of breast cancers express human epidermal growth factor II (HER2) amplification.[1] Trastuzumab is a recombinant DNA-derived monoclonal antibody that selectively binds to the extracellular domain of the HER2 protein in breast cancer cells.[2,3] Trastuzumab therapy is important in the treatment of both early and advanced disease. Five randomized controlled trials have addressed the addition of adjuvant Trastuzumab to chemotherapy in node-positive and high-risk node-negative patients with HER2 overexpression and showed a survival advantage with Trastuzumab.[4–8] Its use, however, results in a small to modest risk for cardiotoxicity, which is typically manifested by an asymptomatic decrease in left ventricular ejection fraction and less often by clinical heart failure.[9–11] The rate of cardiac dysfunction with use of Trastuzumab varied from 1 to 27% in different arms of these trials.[12]

Although the heart was initially thought to be relatively radio-resistant, cardiovascular disease resulting from chest radiotherapy (RT) for therapeutic purposes is now clearly recognized. The majority of the radiation-induced cardiovascular disease has been reported in patients who previously treated with thoracic RT for Hodgkin's disease and breast cancer. Estimated relative risk of fatal cardiovascular events after RT for Hodgkin's disease and left-sided breast cancer range between 2.2 and 7.2 and 1.0 to 2.2, respectively, compared to healthy controls.[13]

Numerous studies of radiation induced toxicity show that endothelial cell injury is the key point in most tissues even though the endothelial cells compromise only a minor fraction of cardiac cells.[14–17] The sequence of endothelial injury, cell detachment, thrombosis and fibrosis result in significant tissue injury that often limits radiation oncologist in attempting to deliver curative doses to a nearby tumor. Steward and Fajardo have demonstrated that damage to the myocardium develops through three phases of injury.[13,18] The acute inflammation phase occurs about 6 h after RT and a neutrophilic infiltrate develops involving all layers of heart. The second phase also known as latent phase in which a slight progressive fibrosis begins about 2 days after exposure. However electron microscopy of the myocardial capillary endothelial cells demonstrates progressive damage leading to obstruction of the lumen and thrombi of fibrin and platelets. Though healthy endothelial cell replication in the vicinity occurred, it is generally inadequate and an inevitable ischemia leads to progressive fibrosis. Animals begin to die at approximately 70th day due to extensive fibrosis. The hallmark of this late stage is extensive fibrosis (Figs. 1 and 2).

For patients with breast cancers that overexpress the HER2 receptor, both RT and Trastuzumab take place in the treatment. In the clinical practice RT and Trastuzumab may be used either concomitantly or sequentially. The risk of toxicity of combined Trastuzumab and RT on cardiovascular structures has not yet been evaluated in detail. There is conflicting data with respect to the cardiac toxicity profile of using concomitant RT and Trastuzumab. Preclinical in vitro and in vivo studies have shown that the cascade of events through the HER2 receptor is involved in tumor radiosensibility,[19,20] application of Trastuzumab concurrently with radiation thus increases the antitumor effect of radiation. There are same clinical evidences in the literature that Trastuzumab also radiosensibilizes human healthy tissues and in this way it could increase the toxicity of the treatment.[21] Currently the most important question remains whether the concomitant therapy with Trastuzumab and RT increases cardiotoxicity of the treatment. In the literature, there are limited data about the safety of concomitant therapy with RT and Trastuzumab.[19] In an experimental study, it was shown that when combined with high dose RT, and Trastuzumab may lead severe vascular damage.[22]

The use of antagonists of the mineralocorticoid receptor (MR) in the treatment of myocardial hypertrophy and heart failure has gained increasing importance in the last years. Steroids, including aldosterone, are able to interact with peptide hormone signaling. The epidermal growth factor (EGF) and its receptor (EGFR) represent one of these signals involving aldosterone. Pathophysiologically, an interaction between Aldosterone/MR and the EGFR signaling pathway was demonstrated by an up-regulation of EGF-induced arterial contraction mediated by mineralocorticoids and a reduction of cerebrovascular remodeling process after ischemia by MR inhibition concomitant decrease in EGFR-mRNA.[23,24] Additionally, the cardioprotective mechanism of Spironolactone was associated with the EGFR[22] and inhibition of Aldosterone synthase was shown to ameliorate angiotensin (ang)-II induced end-organ damage, thus highlighting the significance of aldosterone and the EGFR for general pathophysiology in renocardiovascular system.[25] The underlying mechanism for the genomic interactions seems to be a stimulation of the EGFR promoter by Aldosterone-bound MR, which then leads to dose-dependently enhanced EGFR proteins that can be inhibited by Spironolactone.[26]

2. Aim

In the current study we aimed to evaluate whether the use of spironolactone would be able to ameliorate the cardiac toxicity induced by concomitant Trastuzumab and RT. Our second aim was to determine cardiotoxicity profile of using Trastuzumab and RT concomitantly.