Pentoxifylline and Radiation-Induced Heart Disease

Patients who receive radiotherapy for tumors in the chest may experience radiation-induced heart disease (RIHD). This late and potentially severe side effect of radiotherapy can occur if all or part of the heart lies in the radiation field. Patients particularly at risk include breast cancer patients previously treated with radiotherapy, lung cancer patients, lymphoma patients, and patients with esophageal cancer. RIHD presents clinically several years after the heart has been exposed to radiation. Manifestations of RIHD include accelerated atherosclerosis in coronary arteries and myocardial fibrosis. These symptoms become worse over time and are not naturally resolved. RIHD continues to increase in occurrence partly because of the rapid increase in the numbers of long-term cancer survivors. No current method can prevent or reverse RIHD. Research is therefore urgently needed to develop interventions that can reduce this side effect of radiotherapy to the chest.

Pentoxifylline (PTX, Trental™) was first developed to improve peripheral blood flow. Because of its many anti-inflammatory and anti-fibrotic properties it was soon considered in the treatment of a wide variety of other disorders. Clinical studies have shown beneficial effects of PTX in radiation fibrosis of the skin, lung, and intestine. PTX therefore stands among the few drugs reported to reduce radiation fibrosis. Most studies have tested PTX in combination with the most common form of vitamin E (α-tocopherol), considered to be beneficial through its anti-oxidant properties. We have previously shown that a combination of PTX and α-tocopherol improved cardiac function and reduced cardiac fibrosis in a rat model of RIHD. The proposed project uses these results as a basis to further develop and study PTX and vitamin E as a potential treatment of RIHD.

Vitamin E exists in eight forms: α-, β-, γ-, and δ-tocopherol and α-, β-, γ-, and δ-tocotrienol. Although tocopherols and tocotrienols are mostly known for their anti-oxidant effects, some forms of vitamin E have additional properties. γ-Tocotrienol, for instance, is a potent inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis. It is well known that inhibitors of HMG-CoA reductase can reduce injury from radiation. However, the combined effects of PTX and γ-tocotrienol on RIHD have not yet been studied. We hypothesize that γ-tocotrienol is more effective in reducing manifestations of RIHD than α-tocopherol when administered in combination with PTX.

To test this hypothesis, a rat model of RIHD will be used. Rats will receive local heart irradiation and will be treated with PTX in combination with either α-tocopherol or γ-tocotrienol. The research fellow will be involved in small animal echocardiography to measure the effects of radiation and drug treatment on rat heart function. In addition, histology, immunohistochemistry, western-blots, and real-time quantitative PCR will be used to determine structural and molecular changes in rat hearts obtained from the different treatment groups.