Cardiotoxicity by Tyrosine Kinase Inhibitors: new cellular mechanisms

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Cardiomyocytes and mitochondria represent, respectively, a common cellular and subcellular target of anthracycline and Tyrosine Kinase Inhibitors (TKIs) activity which may explain their toxic effect on high energy consuming organ such as the heart. Similarly, cardiovascular adverse events following more recently introduced anti-cancer drugs such as proteasome inhibitors or immuntherapeutic agents have been preferentially attributed to their interference with differentiated myocardial cells viability.

However, primitive cells with properties of stem cells are present in the myocardium, either as a resident population of embryonic origin or as a blood-born population that continuously seeds the tissue. Thus, two potential sources of progenitors may participate for the continuous renewal of myocytes and coronary vessels throughout the lifespan of an individual. Importantly, this pool of cells are recalled to increase the myocardial mass in response to physiological or pathological demands that impose an enhanced load on the heart.

Experimental observations from our and other laboratories on the human and murine heart strongly suggest that cardiotoxicity involves the detrimental effects of anti-cancer treatment on the biological and functional integrity of resident myocardial progenitor cells. Whether cytotoxic agents preferentially affect differentiated parenchymal cells, primitive cells or both, is a fundamental question. This is because the determining factor in the onset and development of cardiovascular toxicity may be the ability of anti-cancer agents to blunt the proficiency of stem cells to replace damaged cardiomyocytes. Thus, new therapeutic approaches should be devoted to preserve the intracardiac pool of primitive cells in order to favor an appropriate myocardial response for tissue repair. In addition, the systemic effect of cytotoxic drugs on the stem cells of the organism may exert two negative consequences on the myocardium: 1) depletion of the resident cardiac stem cells; and 2) impairment of the ability of bone marrow stem cells to migrate, home and replenish the depleted primitive cell compartment of the heart. Importantly, a relevant emerging issue is to determine whether these adverse effects on the stem cell pool are immune mediated.

Efforts should be made by medical institutions to takle on early and long term deleterious effects of anti cancer therapy by new preventative and therapeutic strategies.