P62 The radiobiological effects of Radium-223 in metastatic prostate cancer cells

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Introduction & Objectives: Nowadays, metastatic castrate-resistant prostate cancer (mCRPC) remains an incurable disease. Radium-223 was introduced in the treatment scheme for this stage of the disease, improving the overall survival and patients' well-being. However, recently it uses became controversy between European Urological community due to the new EMA recommendation for only use Radium-223 as third treatment line. The poor knowledge regarding Radium-223 mechanisms-of-action, as well as the interaction between these particles and cells presents in metastasis has been indicated by different authors as one limitation to improve the applicability of this treatment. Given this, the aim of our project is to study the Radium-223 mechanism of action, namely in terms of kinetics, radiobiologic effects and response pathways activated after irradiation of mPCa cells.

Materials & Methods: Two cell lines of mPCa, PC3 (from bone metastasis) and LNCaP (from lymph-node metastasis) were used. The capacity to 223Ra internalize, keep retained and reach the nucleus of cells was accessed by kinetic assays. Then, survival was measured to determine LD50 value. After this, cells were irradiated with LD50, <LD50 and <LD50 doses of 223Ra and proliferation (SRB assay), oxidative stress (fluorescence), morphological changes (May-Grünwald-Giemsa assay), DNA damage (comet assay), DNA Damage Response (western blot) and in angiogenesis (aortic ring assay) was evaluated.

Results: Results showed that 223Ra reach the nucleus and kept inside the PCa cells. LNCaP cells (LD50 = 1.41mGy) was significantly more radiosensitive than PC3 cells (LD50 = 4.22mGy). Was observed a significant decrease in proliferation, followed by an increase in CHK2(Ser15) expression after irradiation. Comet assay showed that 223Ra leads to DNA strand-breaks, with significant increase in tail moment after DL50 of each cell line. Angiogenesis study showed a decrease in endothelial cell migration and organization. These results were associated with morphological changes characteristics of apoptosis, after LD50 in both cell lines, and an increase in number of LNCaP cells in necrosis.

Conclusions: The radiobiological effects showed that 223Ra acts directly in PCa cells, leading to cytotoxic and anti-proliferative effects on both cell lines, suggesting a decrease in the aggressiveness of tumor cells. Also, a better efficacy in early stages is suggested, as well as the capacity to be used in the treatment of lymph nodes in mCRPC patients. To complete the project more studies regarding the combination of Radium-223 and other drugs that inhibits proteins present at DDR pathways will add valuable information regarding new possible combinations for mCRPC

treatment.

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