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COMPETITION RESPONSE OF PSMA-I&T RADIOLABELED WITH LUTETIUM-177 TO LNCAP, PC-3 AND RWPE-1 CELLS

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A B S T R A C T

Introduction/Justification: 177Lu-PSMA-I&T stands out as a promisor radiopharmaceutical for therapy of prostate cancer based on the specific bind of Glu-urea-Lys pharmacophoric group prostate-specific membrane antigen (PSMA), anchored in the epithelial prostate cell membrane, overexpressed in prostate cancer and increased in metastatic castration-resistant prostate cancer (mCRPC). To study the affinity of 177Lu-PSMA-I&T to target receptor, in vitro competition assay is frequently evaluated. **Objectives:** The purpose of this study was to compare the binding of 177Lu-PSMA-I&T in competition assay to three cell lines. LNCaP and PC-3 are the most used in vitro cell lines studies of prostate cancer research and LNCaP cells are known to have a mutated androgen receptor (AR) (T877A), PC3 is negative for AR expression, and RWPE-1 is frequently used as non-cancerous control. **Materials and Methods:** Radiochemical purity (%RP) of radiolabeling 177Lu-PSMA-I&T was determined by High Performance Liquid Chromatography (HPLC) and Thin Layer Chromatography (TLC) with results of > 95% of main peak and < 3% of free 177Lu, respectively. In vitro assays were performed with LNCaP (ATCC® CRL- 1740, American Type Culture Collection), RWPE-1 and PC-3 (LIM55, FMUSP) cell lines, cultivated in RMPl 1640 medium (Life Technologies, MD, USA) plus 10% v/v Fetal Bovine Serum (FBS) with 100 UI/mL of penicillin and 300 μg/mL of streptomycin. 6-well plates were used, and to each well 2×105 cells. For the total binding, cell incubation medium was removed and replaced with 1 mL of 177Lu-PSMA-I&T (2.22 MBq (60 μCi), approximately 0.076 nmol of peptide, diluted with RMPl 1640 medium/10% v/v FBS) and 1 mL of RMPl 1640 medium, per well. The plates were incubated for 1 h at 37 °C. Cells were washed two times with 1 mL of 0.1 M PBS pH 7.4, followed by an incubation step of 5 minute at room temperature with 1mL ice-cold glycine buffer (0.05 M glycine pH 2.8) and lysed with 2 mL of 1 M sodium hydroxide and incubation step of 10 minutes at room temperature. The same procedure was repeated replacing 1 mL of RMPl 1640 medium with 1mL of competitor (PSMA I&T, molar excess of 7.6 nmol in RMPl 1640 medium). To have the same geometry, the tubes were filled to the same volume (1mL) at each step. An automatic gamma counter with NaI (TI) crystal (D5002 Cobra II, Packard) was used to measure the radioactivity (as cpm) at each tube, and the concentration of 177Lu-PSMA-I&T bonded to the cells was determined in fmol. The assays were performed in quintuplicate for each cell. **Results:** The binding of 177Lu-PSMA-I&T to LNCaP cells showed 1309.3 $\pm$ 176.8 fmol without competitor and 928.5 $\pm$ 84.7 fmol in the presence of competitor, with significant difference (P= 0.0152, GraphPad Prism®). PC-3 cell line showed 28.8 $\pm$ 15.2 fmol without competitor and 25.3 $\pm$ 6.2 fmol with competitor, showing no significant variation (P = 0.6599). The results of binding with RPWE-1 cell line showed 74.3 $\pm$ 6.2 fmol without competitor and 37.9 $\pm$ 7.7 fmol with competitor, a significant difference ($P \leq 0.0001$). **Conclusion:** These results demonstrated the affinity of 177Lu-PSMA-I&T for binding receptors in LNCaP cells and low uptake by PC-3 cells due to the lack of expression of specific receptors. RWPE-1 cell line is positive for AR/PSA mRNA/protein and sensitive to androgens. However, it expresses low levels of PSMA, which likely explains the reduced binding of the radiopharmaceutical.

Keywords: Binding, Lutetium-177, PSMA-I&T, Radiopharmaceutical;.

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SYNTHETIC QUINAZOLINONES AS NEW ANTILEUKEMIC AGENTS

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A B S T R A C T

Introduction/Justification: Acute leukemias are aggressive malignancies characterized by the uncontrolled proliferation of hematopoietic progenitor cells in the bone marrow, leading to impaired production of normal blood cells. Nitrogen heterocycles have attracted the attention of researchers from various fields, with an extensive list of different biological activities. Among the heterocycles, quinazolines stand out, which have been widely investigated for the development of new drugs. **Objectives:** Evaluation of the anticancer activity of quinazolinones against acute leukemic cell lines. **Materials and Methods:** The quinazolinones (A1-A20) were synthesized in the Laboratory of Synthesis of Natural Products and Drugs (Institute of Chemistry, Unicamp). In total 2×104 cells of T cell acute lymphoblastic leukemia (T-ALL), Jurkat, and acute promyelocytic leukemia (APL), NB4, per well were seeded in a 96-well plate in the appropriate medium in the presence of vehicle or different concentrations of compounds (ranged