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ANTIBODY-BASED THERAPIES

1P Is 177Lu-PSMA an effective treatment modality for mCRPC patients with visceral metastasis?

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Background: Metastatic castration-resistant prostate cancer (mCRPC) is the most challenging stage in prostate cancer. Patient with visceral metastasis have the poorest outcome amoung them. In this retrospective study, we analyzed the clinical outcome of lutetium-177 prostate-specific membrane antigen (^{177}Lu-PSMA) in mCRPC patients with visceral metastasis.

Methods: Ten patients of mCRPC with visceral metastasis were enrolled for one cycle of ^{177}Lu-PSMA therapy. Number of efficacy and safety parameters, e.g., prostate-specific antigen (PSA), visual analog scale (VAS) and analgesic quantification scale (AQS), hemoglobin (Hb), total leukocytes counts (TLC), platelets, creatinine, & total bilirubin, were assessed and compared with Wilcoxon signed-rank test. The progression-free survival (PFS) curve was computed by the Kaplan-Meier method. The receiver operating characteristic curve (ROC) was also plotted for ^{177}Lu-PSMA dose. $P \leq 0.05$ was considered significant.

Results: Liver (80%), lung (30%), adrenal (10%), and peritoneum (10%) were the sites of visceral metastasis in our study. On PSA response assessment, 10%, 60%, and 30% of the patients had partial response, stable disease, and progressive disease, respectively. Forty percent of the patients had improvement in the VAS, while 50% had improvement in the AQS score. Median PFS was 24 weeks in our study. A cut-off of 4.88GBq of ^{177}Lu-PSMA was the best-predicted progression with 66.67% sensitivity and 100% specificity on ROC analysis. Thirty percent of the patients showed grade 3 anemia. No other significant toxicity was seen.

Conclusions: Lutetium-177-PSMA was a reasonable palliative treatment option with limited toxicity for these end-stage mCRPC patients with visceral metastasis with adequate PSA stabilization.

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2P Molecular imaging evaluation of a novel Claudin18.2 specific monoclonal antibody labeled with radionuclide

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Background: Claudin18.2 (CLDN18.2), a member of tight junction protein family, is strictly limited to differentiated epithelial cells of gastric mucosa and multiple tumor types, such as gastric, esophageal and pancreatic cancers. We have generated a novel species cross-reactive CLDN18.2 specific antibody, and labeled it with "Next Generation" radionuclide I-124 (^{124}I-18B10).

Methods: I-124 was produced by the medical cyclotron using ^{124}Te (p, n) ^{124}I reaction. In the cell-based assay, the uptake of ^{124}I-18B10 in MKN45-CLDN18.2 (CLDN18.2+ cell line) and MKN45 (CLDN18.2- cell line) were detected at 10, 30, 60 and 120 min, and the blocking group using cold 18B10 antibody to block uptake was also evaluated. PDX-bearing mice, which were selected by immunohistochemical (IHC) method and assessed as CLDN18.2+ or CLDN18.2-, were injected with either 18.5 MBq ^{18}F- fluorodeoxyglucose (^{18}F-FDG), or ^{124}I-18B10, or ^{124}I-hIgG via the tail vein, and Micro-PET/CT images were taken at 2, 60 and 120h post injection.

Results: The specific activity of ^{124}I-18B10 was 0.62 mCi/mg antibody and the labeling rate was higher than 95%. The cell-based assay showed that specific uptake of it by the MKN45-CLDN18.2 cells was significantly higher than that of by the MKN45 cells (23.51±0.47 % vs 8.69±0.35 % at 2 h, $P<0.05$). Both uptake assay and competitive binding assay in the MKN45-CLDN18.2 cells showed that cold 18B10 antibody could significantly reduce the uptake and binding of ^{124}I-18B10 (15.33±0.82 % at 2 h, $P<0.05$). As expected, the uptake of ^{124}I-hIgG was low (5.21±0.29 % at 2 h). In PDX bearing mice, the uptake of ^{18}F-FDG in tumor sites was low. The distribution of ^{124}I-18B10 in CLDN18.2+ PDX bearing mice was increasingly enriched in the tumor sites over time. The uptake signals of ^{124}I-18B10 in CLDN18.2- PDX bearing mice in all tissues and tumors remained similar at different time points.

Conclusions: The ^{124}I-18B10 antibody has good radio-chemical characteristics and stability. The cell uptake assay and competitive binding assay demonstrated that the probe is highly specific to CLDN18.2. Micro-PET images of PDX bearing mice demonstrated that ^{124}I-18B10 was enriched in the lesion of CLDN18.2 positive tumors rather than negative tumors or normal tissues.

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3P Determination of therapeutic effects of multifunctional micelle-based nanocarriers on breast cancer cells

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Background: Breast cancer is the most common and frequent cause of death in women in all types of cancer. Current treatment protocols do not provide a complete cure and targeting therapy can provide an important avenue for successful treatment of breast cancer. In this study, we aim to determine the therapeutic effects of the drug-conjugated carrier system with the conjugation of peptide sequence and antibody on HER2-positive breast cancer cells.

Methods: The selectivity of single nanocarriers were compared with doxorubicin (DOX) loaded-HER2 targeting peptide (LTVSPWY) and DOX loaded-monoclonal antibody (Herceptin®) on HER2-positive and HER2-negative breast cells. After defining the physicochemical characterization of micelle-based nanocarriers, the cytotoxic effects of micelles on healthy breast epithelial cells (MCF-10A, HER2-negative) and breast cancer cells (SKBR3- HER2-positive) were determined by MTT cell proliferation assay. Next, apoptotic and genotoxic effects of micelles (IC50 doses of DOX loaded-peptide conjugated) were determined by using JC-1 assay and Western Blotting (Bax and Bcl-2 proteins) and Commet assay, respectively. Also, drug-releasing was analyzed by flurosance microscopy with imaging processes. Lastly, cytostatic effects of micelles were investigated with cell cycle analysis.

Results: DOX loaded-HER2 targeting peptide (DOX-Pep-HER-2-NCs) and DOX loaded-monoclonal antibody micelles (DOX-Anti-HER-2-NCs) had significant differences. DOX-Pep-HER-2-NCs had more toxic effects on SKBR-3 cells than DOX-Anti-HER-2-NCs. However, there is no significant change after the application of these micelles on MCF-10A cells. Besides, the intracellular amounts of doxorubicin with the application of DOX-Pep-HER-2-NCs were detected as higher in HER-2 positive breast cancer cells after measured by fluorescence imaging. Additionally, DOX-Pep-HER-2-NCs had more apoptotic, cytostatic and genotoxic effects on HER2 overexpressed SKBR-3 cells.

Conclusions: The targeting and therapeutic efficiency of DOX-Pep-HER-2-NCs were compared to DOX-Anti-HER-2-NCs on SKBR-3 cells. DOX-Pep-HER-2-NCs was more effective than DOX-Anti-HER-2-NCs on SKBR-3 cells in terms of targeting and therapeutic effects.

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