REVIEW OF PROSPECTIVE RADIOPHARMACEUTICALS BASED ON PROSTATE-SPECIFIC INHIBITORS OF MEMBRANE ANTIGEN FOR DIAGNOSTICS AND THERAPY OF METASTATIC PROSTATE CANCER

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Prostate cancer (PC) one of the most common oncological diseases. In Russia this disease is found in 60% cases after diagnostics on late stage (3-4), when process of active growth of cancer's cells is inevitable. In 1/3 of patients PC was diagnostied with metastases already present [1-3]. Metastases of prostate cancer are often detected in bone tissue (80-90 % from all localizations), lymphatic nodes (10%), liver and lungs (2.5 %). This localization is nor favorable for radical treatment. Most of this patients (about 60% from all PC cases) die within 1,5 – 2 years from the moment when disease diagnosis was made. Nowdays about 40 thousand of the first case PC are being registered per year in Russian Federation. Brachiotherapy efficiency is 75% effective [2, 3]. Consequently in effect treatment metastatic PC – need about 30 thousand patients every year only on territory of Russia.

Early diagnosis of post-surgical relapses, as well as widespread metastatic prostate cancer and castration-resistant prostate cancer remains an unresolved problem. The complexity of early diagnosis of metastatic foci of prostate cancer leads to a significant decrease in life expectancy of patients after the initial treatment due to the occurrence of local and distant relapses. For example, despite numerous screening programs, in the US, prostate cancer is the second leading cause of death from cancer among men [4, 5].

Prostate-specific membrane antigen (PSMA) is a type II membrane protein is expressed in all forms of prostate tissue, including neoplasms [6]. The expression of PSMA in cancer cells is 100-1000 times higher than in other tissues and normal prostate cells. It is important that the intensity of PSMA expression increases with prevalent metastatic PC, and especially in castration-resistant PC. Unlike PSA, PSMA is not found in the blood. Thus, PSMA is an ideal marker of prostate cancer cells and an excellent target for radionuclide imaging and therapy [7-9]. Given this fact, in the West, radiopharmaceutical kits (RPKs) were developed to visualize PC based on targeted compounds that selectively bind to PSMA on the membrane cancer cells. ^{111}In-capromab was the first clinical radiopharmaceutical (RP) for visualization of PC. Despite good results of visualization of the primary tumor, satisfactory data on the visualization of local and distant metastases were not obtained. In addition, the compound was loosely bound to the PSMA receptor, was slowly excreted from the body and therefore did not provide sufficient coefficients of differential accumulation and, accordingly, a qualitative visualization of metastases [4, 8, 9]. Later, improved RPs with ^{123}I for diagnosis and ^{131}I, ^{177}Lu and ^{90}Y for therapy were developed [7, 10]. However, in spite of the best results of preclinical and pilot clinical trials, in comparison with ^{111}In-capromab, these new RPs have not been clinically used since retained the deficiencies of labeled antibodies: weak interaction with the PSMA receptor, a high background in the blood, and a long waiting time for visualization. In 2009, small peptide molecules PSMA inhibitors characterized by high selective affinity to PC were developed (e.g. (N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-[^{18}F]methyl-L-cysteine[^{18}F]DKPMMC)). These molecules, labeled with ^{18}F, showed satisfactory results in PET diagnostics of [7, 9].

However, the most encouraging results were obtained by two groups of researchers (MIP Cambridge, USA and DNM Heidelberg, Germany) using new small peptide molecules modified with urea with the highest affinity for PSMA. Based on these compounds, new RPs for SPECT (^{123}I, ^{99m}Tc, ^{111}In) and PET (^{18}F, ^{68}Ga, ^{64}Cu) were studied. RPs for radionuclide therapy with ^{131}I, ^{188}Re, ^{177}Lu, ^{90}Y were studied as well. A distinguishing feature of these compounds is favorable pharmacokinetics, a high and prolonged accumulation in tumor and metastases, rapid excretion from the body, which provides high value of the differential accumulation factor, and high-quality rendering of small tumor foci [10-12].

Then new ^{99m}Tc-PSMA and ^{188} Re-PSMA RPs were developed. The results of the clinical studies showed that these RPs quickly visualize the tumor and its metastases, including ones in lymph nodes and skeleton [10-12]. Currently, ^{68}Ga and ^{177}Lu PSMA-based radiopharmaceuticals are being extensively studied [13], but also are being used in routine clinical practice in some countries.

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