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"Image and Treat" – An Individualized Approach to Urological Tumors

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Abstract

Purpose of review—The current treatment options for advanced urologic cancers demonstrate limited efficacy. To obtain optimal clinical results, there is a need for new, individualized, therapeutic strategies, which has only recently been applied to these malignancies. Nuclear medicine plays an increasing role in establishing imaging biomarkers necessary for personalized medicine. This review focuses on the current status of the "image and treat" approach combining molecular imaging with targeted radionuclide therapy of urological malignancies

Recent findings—Tumour-specific targets in uro-oncology are showing promising results for development of personalized therapy using positron emission tomography/computed tomography (PET/CT) molecular imaging and radioimmunotherapy (RIT). The antibody cG250, which binds to carbonic anhydrase IX (CAIX), is being evaluated as a radiolabelled imaging and therapeutic agent in clear cell renal cell carcinoma (ccRCC). ^{124}I -cG250 PET/CT has demonstrated excellent targeting of ccRCC. Prostate specific membrane antigen (PSMA) is a promising target for both PET/CT and RIT of prostate cancer. HER2 may be another potential target in bladder and prostate cancer.

Summary—Tumour-specific targets and biomarkers are being studied for PET/CT and RIT. This may lead to development of new therapeutic strategies. However, considerable investment in new research will be required for personalized medicine to be routinely used in uro-oncology.

Keywords

positron-emission tomography; radioimmunotherapy; PSMA; CAIX; G250; HER2 receptor

Introduction

Tumour resistance and toxicity to normal tissues limit the efficacy of conventional anti-cancer treatments such as radiation and chemotherapy. The systemic side effects of chemotherapy in particular represent a severe problem. The most promising alternative to conventional therapy is *targeted tumor therapy* where selective molecules are used to direct anti-cancer drugs to the

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tumor, thereby limiting the damage to healthy tissue. For targeted tumor therapy, peptides and antibodies possess a key position as drug delivery vectors [1]. To kill the targeted tumour cells, the favourable targeting properties of antibodies and peptides must be combined with an efficient cytotoxic moiety such as toxins, drugs, or therapeutic radioactive nuclides. *Targeted radionuclide therapy (TRT)* uses the latter as a local source of radiation to combine the favourable targeting properties of peptides and antibodies with the effectiveness of radiation-induced cell death [2;3]. A major advantage of TRT is the possibility to determine the selective accumulation in the targeted tissue by molecular imaging studies via single photon computed tomography (SPECT) or positron emission tomography (PET) using structurally identical diagnostic compounds. For this purpose, targeting of epitopes that are expressed even in relatively low concentrations is feasible. These non-invasive imaging methods allow estimation of radiation dose distribution prior to therapy, tumour staging, and early monitoring of the efficacy of individual treatments. This novel class of pharmaceuticals offers the potential to develop patient-specific therapies based on the new “image and treat” approach.

The current treatment options for advanced urologic cancers demonstrate limited efficacy and severe side effects [••4,•5,••6,7]. Therefore, there is a need for new therapeutic strategies. The idea of individualizing therapies to obtain optimal clinical results is not new but has only recently been applied to urological malignancies. This review focuses on the recent advances of molecular imaging as applied to TRT in uro-oncology.

Molecular imaging and targeted radionuclide therapy

In recent years there has been much focus on personalized medicine, where pharmaceutical therapies are tailored to the particular characteristics of the individual patient. The role of molecular imaging in personalized medicine, using targeted drugs in oncology, is very attractive. It provides *in vivo* regional information before and, in real time, during treatment, which cannot be obtained by *in vitro* methods (“regional proteomics”). In clinical practice, imaging biomarkers may be used to screen for cancer, confirm diagnosis, assess extent, and predict response to available therapies [8]. Nuclear medicine plays an important role in establishing imaging biomarkers in clinical decision-making. ^{18}F-fluorodeoxyglucose (FDG), the first PET molecular imaging biomarker, is a biomarker of glucose metabolism. Most cancer cell types demonstrate increased glucose metabolism leading to increased ^{18}F-FDG uptake. ^{18}F–FDG PET/CT is now widely used in the management of several cancer types. In uro-oncology, PET/CT has been one of the slowest areas to develop. This is mainly due to urinary excretion of ^{18}F–FDG and low ^{18}F–FDG uptake especially in prostate and some renal cancers. However, the role of PET/CT in uro-oncology is likely to expand as new and more favourable tracers are evaluated [9]. New biomarkers that image cell proliferation, apoptosis, angiogenesis, hypoxia, and growth factor receptors are being studied [10], and may lead to enhanced clinical management of cancer patients.

Radiolabelling of modified forms of the imaging biomolecules with therapeutic radionuclides allows therapeutic applications using radioconjugates that are almost identical to the imaging probes. In contrast to chemotherapy, TRT requires very low mass amounts of the targeting compound. *Peptide receptor radiation therapy (PRRT)*, as one form of TRT, is based on site-specific accumulation, preferentially due to receptor-mediated endocytosis and intracellular retention of radiolabelled peptides [10;11]. At present, PRRT is mainly used for the treatment of neuroendocrine tumours [12]. The somatostatin receptor-binding agents ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE are examples of successfully applied oncological PRRTs [2;3;13]. In *radioimmunotherapy (RIT*), antibodies are labelled with radionuclides for therapy. ^{90}Y-rituximab (Zevalin®, Biogen, IDEC, Cambridge, MA) and ^{131}I-tositumomab (Bexxar®, Corixa, Seattle, WA, USA) are examples of radiolabelled antibodies for cancer treatment [••13]. These two therapeutic agents target the CD20-antigen on B-cells.

The therapeutic effect of TRT is achieved primarily by ionization radiation of the radionuclide, and the therapeutically effective radiation dose is determined by the physical characteristics of the radionuclide. As the radiation is not restricted to the targeted cell, it may also affect all tumor cells in its range. This effect, called “bystander” or “crossfire” effect, is particularly important for treatment of tumors with heterogeneous antigen or receptor expression or insufficient vascularization [2]. The most common nuclides that are currently used for endoradiotherapy are β-emitters such as ^{131}I, ^{177}Lu, and ^{90}Y. Medium-energy β-emitters, i.e., ^{131}I and ^{177}Lu, are more effective for the treatment of small tumors [2;3]. In larger tumors, isotopes emitting high-energy β-radiation, like ^{90}Y, might present a better alternative. Molecular imaging plays an essential role in balancing the clinical benefits and risks of TRT. To effectively treat individual patients, careful assessment of biodistribution, dosimetry, and toxicity of the therapeutic radionuclide is essential.

Carbonic anhydrase-IX

Renal cell carcinoma (RCC) is the third most common genitourinary cancer site after prostate and bladder cancer [•14]. Imaging plays an important role in the clinical management of RCC [••15]. However, RCC is a radio- and -chemotherapy resistant tumor, and current treatments have limited efficacy, resulting in high morbidity and mortality in patients with metastatic disease [4]. Thus, there is a need for new therapeutic strategies in RCC. Monoclonal antibodies targeting tumor-associated antigens have been developed for RCC [4;16], and targeted agents are being used increasingly for the treatment of metastatic RCC [17;18]. Among them, targeting of carbonic anhydrase IX (CAIX) antigen using monoclonal chimeric G250 antibody (cG250) is a new approach for imaging and treating RCC. CAIX is ubiquitously expressed in more than 90% of clear-cell RCC (ccRCC) but not in normal kidney [16;19–21]. In addition, high expression of CAIX appears to be a marker of poor prognosis in ccRCC [20;22].

cG250 PET

The antibody G250 has been studied in ccRCC both as a murine antibody and a chimeric antibody (cG250) [23]. For molecular imaging, radiolabelled cG250 demonstrates excellent visualization of known metastatic lesions, and frequently also detects new lesions in patients [24–28]. Recently, ^{124}I-cG250 has been used for evaluating RCC. Divgi et *al.* assessed whether ^{124}I-cG250 PET could predict for ccRCC in 26 patients with renal masses [28]. Surgery was scheduled one week after ^{124}I-cG250 infusion. PET/CT scanning was performed within 3 h before surgery. In this series, ^{124}I-cG250 PET accurately identified 15 of 16 ccRCC, and all nine non-clear-cell renal masses were negative for the tracer. The sensitivity of ^{124}I-cG250 PET was 94%, the negative predictive value was 90%, and specificity and positive predictive accuracy were both 100%. Currently, a multicenter trial in a larger group of patients is being conducted to evaluate the role of ^{124}I-cG250 PET/CT in patients with renal masses [23]. ^{124}I-cG250 PET/CT may be a valuable tool in diagnosing metastases in patients with a G250 positive primary tumor and/or in the differential diagnosis of suspect kidney lesions, i.e., distinguishing ccRCC from other subtypes. Preoperative identification of tumor type could have important implications for the choice of treatment.

CAIX is associated with hypoxia, and expression of CAIX is regulated by the hypoxia-inducible factor 1α (HIF-1α) [29]. Recently, Lawrentschuk et *al.* used in-vivo studies for investigation of hypoxia and CAIX expression in a RCC xenograft model with oxygen tension measurements and ^{124}I-cG250 PET/CT [••30]. ^{124}I-cG250 PET/CT demonstrated excellent tumor targeting, and a correlation between tracer uptake as measured by standard uptake value (SUV) on non-invasive PET/CT studies and traditional biodistribution studies was demonstrated. However, no significant correlation between CAIX and hypoxia was found.

cG250 radioimmunotherapy

The first G250 investigated for RIT in ccRCC were murine antibodies, which can cause an immune response in humans. The production of human-anti-mouse-antibodies (HAMA) inhibits the effectiveness of the second administrated dose of radiolabelled antibody [3]. In a Phase I/II RIT study, escalating activity doses of ^{131}I-G250 were administrated to patients with metastatic RCC [31]. Seventeen out of 33 patients showed stabilization of disease progression. However, all the patients developed a HAMA response. After development of the chimeric form of G250, ^{131}I-cG250 was tested in clinical trials [25;32;33]. The maximum tolerated dose (MTD) of ^{131}I-cG250 was determined in a phase I trial in patients with advanced metastatic RCC [24]. The MTD was determined to be 2220 MBq/m^2, with hematological toxicity being the dose-limiting factor. Divgi et *al.* performed fractionation of the dose in a Phase I study [33]. Steffens et *al.* investigated the effect of two sequential high doses of ^{131}I-cG250 [25]. Five of the 18 patients evaluated had stabilization of their disease, lasting 3–12 months. However, no partial or complete responses were seen.

Radionuclides other than ^{131}I may enhance the therapeutic index of radiolabelled cG250. In order to optimize cG250 RIT, the therapeutic properties of cG250 labeled with four different radionuclides were tested in mice with ccRCC xenografts [34]. The results of the in vivo study indicated that ^{177}Lu- and ^{90}Y-cG250 conjugates may be superior for RIT compared to ^{131}I conjugates. Currently, a phase I/II trial is ongoing, investigating the efficacy of ^{177}Lu-DOTA-cG250 in patients with advanced RCC (NCT00142415). Preliminary results demonstrate excellent tumor targeting of RCC lesions and indicate that ^{177}Lu-cG250 treatment can stabilize previously progressive metastatic RCC [35].

Prostate specific membrane antigen

Prostate cancer is the most common cancer in US men, and is the second leading cause of cancer death in men in the United States [•36]. Imaging is important in the clinical management of prostate cancer patients [••37]. Treatments range from surveillance to radical local treatment to androgen-deprivation therapy [7]. Since there are no effective treatments for advanced prostate cancer, new strategies have to be considered [36]. Several cell surface proteins, glycoproteins, receptors, enzymes, and peptides have been proposed as potential targets for the treatment of prostate cancer [38;39]. Among these, the prostate specific membrane antigen (PSMA) represents an attractive target for molecular imaging and therapy [•40]. PSMA is specifically expressed on prostate epithelial cells, and is strongly up regulated in prostate cancer, with highest expression occurring in androgen insensitive or metastatic disease [•41]. PSMA is not secreted or released into the circulation unlike prostate specific antigen (PSA), which makes it an excellent target for diagnostic and therapeutic agents.

PSMA imaging

The first commercial monoclonal antibody (mAb) against PSMA was 7E11, which is used in the FDA-approved ^{111}In-CYT-356-based imaging of prostate cancer (ProstaScint) [42]. The 7E11 antibody targets an intracellular epitope of PSMA, and therefore binds only to permeabilized necrotic cells [41]. Another anti-PSMA mAb, J591, which binds to an epitope on the extracellular domain of PSMA [43], presents a better alternative for targeting of prostate cancer. J591 had been extensively studied in preclinical models, and demonstrated high tumor-to-normal tissue ratios in prostate cancer xenografts [44;45]. These studies were followed by several clinical trials using J591 labelled with different nuclides for radioimmunoscintigraphy and RIT [46–48] that confirmed the feasibility of J591 as a prostate cancer-targeting agent (see **PSMA radioimmunotherapy** below).

Recently, other mAbs that target PSMA for molecular imaging have been developed. Elsässer-Beile et *al.*, reported the development of three IgG mAbs (3/A12, 3/E7, and 3/F11) with affinity for PSMA [49]. Wolf et *al.*, demonstrated that 3/A12, 3/E7, and 3/F11 bind to different extracellular epitopes of PSMA [•50]. Elsässer+-Beile et *al*, used ^{64}Cu-3/A12 for PET imaging in a prostate cancer xenograft model [••51]. PET was performed 3, 24, and 48 h after injection of ^{64}Cu-3/A12, and good tumor-to-background ratio was found. PSMA-negative tumors were negative on PET. Low-molecular-weight, radiopharmaceutical-based imaging agents may provide superior pharmacokinetics for imaging than radiolabelled antibodies characterized by long circulation time and delayed clearance from non-target tissues [52]. Recently, low-molecular-weight agents that target or inhibit PSMA have demonstrated promising results [53;54;54–56,••57]. Foss et *al.*, showed successful imaging of xenografts that express PSMA using PET and the radiolabelled PSMA inhibitor N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-S-[11C]methyl-l-cysteine (DCFBC) [54]. Mease et *al.*, extended that work by preparing and testing a PSMA inhibitor of the same class labelled with ^{18}F [53]. Biodistribution and imaging studies showed high uptake of ^{18}F-DCFBC in the PSMA positive tumors with little to no uptake in PSMA negative tumors. Hillier et *a*l., reported that two small molecule inhibitors targeting PSMA, MIP-1072 and MIP-1095, exhibited high affinity for PSMA [••57]. The uptake of ^{123}I-MIP-1072 and ^{123}I-MIP-1095 in prostate cancer xenografts was shown by SPECT/CT.

PSMA radioimmunotherapy

Prostate cancer represents an attractive target for RIT for several reasons: 1) the prostate gland is a nonvital organ, thereby allowing targeting of tissue-specific antigens, 2) metastases from prostate cancer are mainly localized in lymph nodes and bones, locations with good access to circulating antibodies, 3) the metastases are often small enough to ensure good antibody penetration, and 4) the serum marker PSA can be used for monitoring of therapeutic efficacy [40–42;58]. In RIT, myelotoxicity due to bone marrow radiation-absorbed doses (Bmrad) is frequently the dose-limiting factor that determines the maximum tolerated dose (MTD). In a dose-escalation study, prostate cancer patients (n=28) were treated with either ^{90}Y- or ^{177}Lu-labelled J591 antibodies [59]. Myelotoxicity after treatment with ^{177}Lu-J591 could be predicted on the basis of the radioactive dose administered or the Bmrad. In contrast, no correlation between myelotoxicity and ^{90}Y-J591 dose was found. In a phase I trial, the MTD of ^{177}Lu-J591 was found to be 70 mCi/m^2 in advanced prostate cancer patients [60]. Multiple doses of 30 mCi/m^2 were well tolerated, and excellent targeting of known metastases was demonstrated.

In a recent study by *Pandit-Tascar et al.*, 14 patients with metastatic prostate cancer received escalating doses of ^{111}In-J591 in a series of administrations, each separated by 3 weeks [48]. ^{111}In-J591 correctly localized 93.7% of the bone lesions detected by conventional imaging. In the study, the optimal antibody mass for RIT was determined to be greater than or equal to 50 mg. Recently, *Tagawa et al.* showed in a phase II trial that a single dose of ^{177}Lu-J591 was well tolerated, and with reversible myelosuppression. In the study, anti-tumor activity was demonstrated in patients with advanced metastatic castrate-resistant prostate cancer, and excellent targeting of known sites of metastases was seen in 97% (31/32) of the patients [47].

HER2

Overexpression of the HER2 protein and amplification of the HER2 gene have been implicated in tumor development, progression, and poor prognosis in several types of cancers [61]. There is increasing evidence that HER2 also plays a role in advanced prostate cancer [62–64] and bladder cancer [65;66]. In prostate cancer patients, HER2 expression is associated with disease progression and androgen independence [62;63], and preoperative plasma HER2 is associated with cancer progression after prostatectomy [62;64]. Caner et *al.*, found that 61.1 % of high-grade urothelial carcinomas demonstrated HER2 overexpression [67]. Recently, Laé *et al*

demonstrated in a large study (n=1005) that 9.2 % of invasive bladder carcinomas are HER2 positive [66]. Therefore, HER2 represents a potential target for both molecular imaging and therapy in HER2 positive bladder and prostate cancers.

HER2 imaging

Monoclonal antibodies such as trastuzumab and pertuzumab, or small scaffold Affibody molecules, are used as HER2-targeting agents [61]. For imaging purposes, these agents are labelled with positron- or gamma-emitting radionuclides for PET or SPECT imaging, respectively [61;••68,69,70–73]. There is increasing evidence that Affibody molecules or other small non-immunoglobulin based tracers have the best potential for developing high-contrast imaging agents to visualize HER2 in vivo compared to full-length monoclonal antibodies [61;72]. *Kramer-Marek et al.* have radiolabelled a HER2-binding Affibody molecule with ^{18}F for in vivo monitoring of HER2 expression by PET [73]. Recently, Kramer-Marek et *al.* also demonstrated that the same tracer can be used for PET/CT imaging to assess changes in HER2 expression following therapeutic intervention [••74]. Baum et *al.* used HER2 Affibody molecules labelled with ^{111}In or ^{68}Ga, and demonstrated high quality SPECT and PET/CT imaging of HER2 positive xenografts [75]. It was possible to detect even very small malignant lesions. *Cheng et al.* also found PET imaging of HER2 expression promising in a xenograft tumor model [71]. Currently, an ongoing trial is evaluating the role of ^{111}In-CHX-A DTPA Trastuzumab imaging for HER2 expression in breast cancer patients (NCI-07-C-0101).

HER2 radionuclide therapy

For therapy, the targeting vector (trastuzumab, Affibody molecules) has been labelled with radionuclides suitable for therapy [72;76,•77,78–79]. Tolmachev *et al.* labelled a HER2-specific Affibody molecule with ^{177}Lu for radionuclide therapy of HER2-positive microxenografts. The results indicate that HER2 RIT may be promising for the treatment of HER2-expressing malignant micrometastases [76]. This strategy, involving assessment of target presence (HER2 positive cancer) and distribution in an individual patient, followed by optimized HER2-specific radionuclide drug delivery, has the potential to improve therapeutic outcome of HER2 positive cancers while reducing side effects.

CONCLUSION

The aim of today's state of the art molecular imaging is detection of the very early stages of cancer, followed by therapeutic action. Molecular imaging may provide unique means for the selection of patients who may benefit from targeted therapies, as well as allow monitoring of early responses to treatment, and enable subsequent restaging. A considerable amount of effort has been focused on the development of personalized medicine in oncology. In recent years, tumour-specific biomarkers have proven to be potentially useful in the development of new therapeutic strategies in uro-oncology. However, considerable investments in research are still required for personalized medicine to be fully developed and implemented clinically.

Abbreviations

BMrad	bone marrow radiation-absorbed doses
CAIX	carbonic anhydrase IX
ccRCC	clear cell renal cell carcinoma
CT	computerized tomography
FDG	fluorodeoxyglucose

HAMA	human-anti-mouse-antibodies
mAb	monoclonal antibody
MTD	maximum tolerated dose
PET	positron emission tomography
PPRT	peptide receptor radiation therapy
PSMA	prostate specific membrane antigen
RCC	renal cell carcinoma
RIT	radioimmunotherapy
SPECT	single photon computed tomography
TRT	targeted radionuclide therapy

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