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Minireview

Theranostic Radiopharmaceuticals : at the Inflection Point

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Abstract

There has been a surge of interest in the field of "theranostic" (therapeutic + diagnostic) radiopharmaceuticals, both clinically and commercially. The potential has arguably been evident for several decades but there have been some hard-learned lessons and some astonishing failures that have contributed to a lack of traction for the nuclear medicine industry. There is evidence that this has now changed and recent product development, clinical outcomes and commercial focus have given the field a much-needed boost. In this article we explore the issues and opportunities that currently define the field. We take the position that we are at the point where such a cost-effective and clinically beneficial precision medicine strategy has reached an inflection point on its trajectory toward success.

Radiopharmaceutical's Dark Past

Until very recently, therapeutic radionuclides failed to disrupt the clinical oncology community with the possible exception of radioiodine therapy in thyroid cancer, nuclear medicine's time-tested success story. However certain products proved to be at least as clinically effective as conventional immunotherapy or chemotherapy approaches. This is no better illustrated than by consolidation radioimmunotherapy (after first-line therapy) in patients with follicular lymphoma. In a phase III study using radioimmunotherapy with ^{90}Y-ibritumomab tiuxetan (Zevalin®) a significant progression-free survival (PFS) benefit of 23.2 months was observed (36.5 vs 13.3 months) [1].

In a phase III trial for rituximab maintenance therapy, a significant PFS benefit was observed at 36 months (74.9% vs 57.6%) for the observation group [2]. Both strategies demonstrated favorable cost-effectiveness profile to prevent disease progression when compared to observation following frontline therapy [3]. However, considering that rituximab maintenance needs 13 to 16 administrations over a period of 2 years versus a single infusion for Zevalin®, there is undeniably a beneficial impact on clinical workflow and patient management [4]. Despite this benefit, Zevalin® and Bexxar® are commercial failures, undermined by inefficient marketing to medical oncologists and competition for patient ownership between medical and radiation oncology (and commensurate revenue). In short, nuclear medicine's failure to integrate with mainstream oncology doomed a product otherwise beneficial to patients.

The Zevalin® case study in the treatment of follicular lymphoma has a genuine risk of being the prototype for all applications of radionuclide therapy in terms of integration with standard care. For example in prostate cancer, nuclear medicine's (highly effective) current "darling" must be integrated with other therapeutic modalities such as chemotherapy, androgen deprivation therapy and possibly immunotherapy in order to be part of changing the standard of care.

The Opportunity Today

To move forward from the failures of Bexxar and Zevalin, five ? key focus areas present enormous opportunity for the nuclear medicine industry. All of these trends fundamentally serve to make "theranostic" techniques a more effective - and accepted - armamentarium for mainstream oncology.

Demonstrating Clinical Benefit

Over the past decade multiple targeted radiopharmaceutical agents have demonstrated clinical benefit for patients with limited therapeutic options. For example, in a phase III clinical trial of ^{177}Lu-Dotatate for patients with advanced and progressive midgut neuroendocrine tumor (NET), the estimated rate of PFS at month 20, was 65.2% as compared with 10.8% in the control group treated with the standard of care octreotide [5]. Despite a relatively low response rate of 18%, although much higher than 3% in the control group, there appears to be an impressive survival benefit. The toxicity profile ^{177}Lu-Dotatate is also excellent with fewer than 10% grades 3-4 AEs and no

real evidence of renal toxicity, irrespective of nephroprotection strategies.

Arguably 2013 was a pivotal year for radionuclide therapy with the published results of a phase III trial with ^{223}Ra-dichloride (Xofigo®, Bayer AG), the first alpha-emitting radionuclide to achieve significant clinical use in oncology [6,7]. The final analysis of the ALSYMPCA study involving 921 patients confirmed a overall survival (OS) gain of 3.6 months with regard to the control group (median, 14.9 months vs. 11.3 months). Moreover no significant difference in the frequency of grade 3 or 4 adverse events were observed with regard to the control group. However ^{223}Ra-dichloride is not a targeted agent and does not bind directly to tumor cells, rather it works indirectly through binding to newly formed bone stroma in proximity to bone metastases. As such, patients with radiographically detectable visceral metastases are counter-indicated.

This is a great limitation because the patients with bone metastasis only and who are eligible for treatment with Xofigo represent less than 50% of the population of mCRPC patients, and with improved imaging that is able to detect small lesions, this patient pool is likely to shrink further. In a recent analysis combining results of ten phase III prostate cancer trials, including almost 9,000 patients with mCRPC, the percentage of patients not presenting with visceral metastases, using standard radiographic techniques, was 42.9% [8]. However there is an important unmet need for treatment of patients with visceral metastases who have a bad prognosis of overall survival. That is the reason why there is a need for radiopharmaceutical agents against cell-surface targets such as Prostate Specific Membrane Antigen (PSMA) capable of irradiating both bone and visceral metastases.

A humanized anti-PMSA antibody (huJ591) labeled with ^{177}Lu has been used for over a decade in multiple phase I and phase II clinical studies for treatment of patients with metastatic castrate-resistant prostate cancer. The results of a phase II clinical study conducted in 47 patients after a single injection of 65-70 mCi/m^2 (2405-2590 MBq/m2) showed a 36% PSA decline with manageable grade 3-4 thrombocytopenia in 66% and neutropenia in 61.7% of patients. Aggressive dosing in this patient population resulted in improved survival as observed in the 70 mCi/m^2 cohort as compared with the 65 mCi/m^2 cohort (median OS = 21.8 months vs. 11.9 months respectively, P = 0.03) [9]. This demonstrates the clinical importance of running proper MTD studies, particularly for solid tumour indications.

Unlike hematologic cancers, solid tumours such as prostate cancer and NET require repeat dosing to achieve clinical efficacy. Using fractionated doses of ^{177}Lu- huJ591 anti-PSMA antibody instead of single doses, a quite interesting dose-response was observed [10]. At the recommended fractionated dose of 40 mCi/m^2 x2 or 45 mCi/m^2 x2 injected 2 weeks apart in 28 patients with metastatic castration-resistant prostate cancer (mCRPC), the median OS was 42.9 months as compared to 14.6 months in 16 patients injected with lower fractionated doses.

Similarly encouraging clinical results have been obtained in a retrospective multicenter study performed in 145 mCRPC patients treated with ^{177}Lu-PSMA-617, a small peptide-like molecule targeting also targeting PSMA [11]. The advantage of rapidly clearing small molecules is that despite a relatively high injected cumulative activity (average dose of 5.9 GBq ranging from 2 to 8 GBq), hematological toxicity is generally less than the longer-circulating antibody-based approach (Grade 3-4 in 12 %). Within the short median follow-up of 16 weeks, no grade 3-4 nephrotoxicity was observed and mild to moderate salivary gland toxicity occurred in 8% of patients. A much longer follow-up will be necessary before establishing the real renal and salivary gland toxicity. The overall biochemical response rate was 45% after all therapy cycles. Due to the short follow-up time no data was available for gain survival.

More recently in a retrospective study in 104 patients pretreated with at least one line of chemotherapy and treated with 351 cycles of ^{177}Lu-PSMA-617, the median OS was 14 months [12]. In another retrospective study performed in fifty-two patients treated with a total of 190 cycles (3-6 cycles per patient) of the same 177Lu-PSMA-617 radiopharmaceutical the median overall survival was 15 months in all patients [13]. It was significantly longer for patients that showed any PSA decline after the first cycle compared to patients without PSA decline (17 vs. 8 months). Although the peptide-base approach has a somewhat better hematologic toxicity profile, the overall efficacy may be lower. The phase III VISION Study is on going, assessing ^{177}Lu-PSMA-617 in Metastatic Castrate-Resistant Prostate Cancer (mCRPC) patients. The primary objective of this study is to compare OS in patients with progressive PSMA-positive mCRPC who received ^{177}Lu-PSMA-617 in addition to best supportive/best standard of care versus patients treated with best supportive/best standard of care alone.

The adoption rate of NET and PSMA theranostics has been unnecessarily slow. The reason is precisely the (mostly) retrospective analysis of small and statistically marginal academic studies, mostly conducted in salvage patients under compassionate use. This cannot be the way forward to gain the interest and trust of the oncology community. As discussed at the end of the article, the clinical and commercial rewards for investing in properly designed trials are significant.

Rise of ImmunoPET Imaging

The clinical efficacy of a radiopharmaceutical depends on tumor uptake and it has been demonstrated that this quantitative uptake is dependent on target expression level [14]. In a recent study focusing on PSMA expression in prostate cancer a significant number of primary tumors and metastases presented with highly heterogeneous PSMA expression levels with a small number of primary and metastatic tumors showing a negative immunostaining (less than 10% positive tumor cells) [15]. Consequently such negativity or heterogeneity of expression may significantly limit the access of a radiolabeled anti-PSMA antibody or peptide to the tumor target cells resulting in therapy failure. Therefore the determination of cell surface PSMA positivity is of major impact.

Screening of tumour phenotypes requires biopsy, a procedure that is invasive and limited to accessible tumour sites. Moreover, it is difficult to obtain repeated biopsies from the same lesions to explore changes in the tumour micro-environment during therapy. There is therefore the need for new nonin-

vasive diagnostic technologies such as molecular imaging to assess whole-body tumor phenotypes to allow more specific therapeutic strategies to be developed. This is the role of immunoPET using the same antibody or peptide as for therapy and labeled with an appropriate positron-emitting radionuclide such as zirconium-89, iodine-124, copper-64 or gallium-68 [16]. Consequently, treatment strategy for individual patients could be tailored by using this quantitative imaging technique. Today, ^{68}Ga-PET is used to select NET patients before radionuclide therapy targeting somatostatin receptors. A few clinical studies have shown that immunoPET with ^{89}Zr- anti-HER2 mAbs can noninvasively identify HER2-positive lesions and is able to predict response to anti-HER2 antibody-based therapy [17]. Similar clinical studies have been performed with other antibodies such as ^{89}Zr-bevacizumab, ^{89}Zr-cetuximab and ^{89}Zr-fresolimumab with for some of them a trend for a correlation between tumor uptake and progression free survival or overall survival after treatrment. ^{89}Zr has become very popular in these applications because of simple chemistry, a reasonable dosimetry profile and growing commercial availability.

A recent clinical study demonstrated impressive tumor responses in patients progressing on enzalutamide and treated with anti-PD1 antibody [18] despite known paucity of PD-L1 expression in prostate cancer [19]. Consequently it may be very important to non invasively detect PD-L1 expression using immunoPET in order to select patients for PD-1 inhibitor therapy. Several preclinical and clinical studies demonstrated the feasibility of this immunoPET approach [20-24]. These examples all serve to demonstrate the possible impact of nuclear-based imaging approaches to enhance not only the patient management of therapeutic radiopharmaceuticals but also other important classes of targeted oncology drugs.

Improved Utility and Supply Chain

Iodine-131 has been routinely used for decades for treatment of thyroid cancer and other cancers after labeling of varied molecules, but patients had to stay for a few days, at least in Europe, in shielded rooms due to a high abundance of energetic gamma emission. This has been a contributing factor to keeping therapeutic nuclear medicine procedures relatively niche.

For new applications, ^{131}I has been somewhat replaced by ^{177}Lu, which has more favorable radiophysical properties and easier conjugation chemistry [25]. It is likely that this radionuclide will enjoy widespread use over the next decade. It can be easily available with high activity levels and high specific activity for a widespread clinical use through global chain suppliers. Although ^{177}Lu was initially available containing a small amount of its long half-life metastable nuclide, non-carrier added (NCA) ^{177}Lu has emerged as the industry standard, with a far better safety and waste management profile.

The chemistry of ^{177}Lu allows easy and stable radiolabeling of varied molecules, including peptides and antibodies, through well-understood bifunctional chelating agents such as DOTA. The relative low energy of emitted beta particles ensures a low handling dose to the radiopharmacy staff and the relatively long half-life enables efficient centralized manufacturing and distribution.

The Rise of Alpha Therapy

In addition to the success of ^{177}Lu, a new generation of alpha-emitters are showing promise and are likely to more successfully engage the pharmaceutical industry because of their more conventional “drug-like” properties in terms of packaging, administration and ambulatory radiation profile.

The high linear energy transfer of alpha particles of about 100 keV/μm is far higher than that of beta-emitting radionuclides and consequently kill isolated cancer cells far more efficiently via an almost thousand-fold increased probability of causing double strand breaks. However the short trajectory length of these particles limit the cell killing radius to less than 100μm. Thus the best clinical target for alpha-therapy may be residual disease after frontline efficient therapy and also cancers that tend to present with smaller tumors such as early prostate cancer biochemical recurrence and metastatic testicular cancer.

A limited number of alpha-emitting radionuclides are available for therapeutic applications. ^{213}Bi was the first radionuclide used in early 2000s in a clinical study for treatment of patients with myeloid leukemia [26]. A humanized anti-CD33 antibody was radiolabeled using the bifunctional chelating agent SCN-CHX-A-DTPA. This study demonstrated the safety, feasibility and antileukemic effects, and was the first proof-of-concept for systemic targeted alpha particle immunotherapy in humans. A limited number of clinical proof-of-concept studies have been conducted using ^{211}At [27-29], ^{212}Pb [30] and more recently ^{225}Ac [31].

We contend that there are, at present, six reasonably robust alpha emitter candidates for routine clinical use over the next decade. Their availability depends on their mode of production and the chemistry needed for radiolabeling and their medical use depends on their half-lives, the presence of daughter nuclides in their decay chain and the challenges of waste management and recycling. Four of them, ^{211}At, ^{225}Ac, ^{212}Pb and ^{213}Bi are fairly readily available for clinical studies and their production capabilities are expected to improve in the coming years. ^{211}At can be produced in a 30 MeV cyclotron by irradiation with an alpha beam of a ^{209}Bi target that is abundant and cheap. ^{225}Ac has several production routes but is presently obtained as a decay product from a limited stock of ^{229}Th. Larger quantities could be available in the future through irradiation of a (reasonably available) ^{232}Th target with a high energy (>100 MeV) proton beam or through irradiation of a radioactive ^{226}Ra target with a 18 MeV proton beam. ^{212}Pb is presently available through a stock of ^{232}Th and a challenging separation chemistry that has been developed in few laboratories and companies. ^{213}Bi can be obtained from an ^{225}Ac/^{213}Bi generator but its short half-life limits its interest.

The slightly more exotic but still clinically promising alphas include ^{227}Th and ^{149}Tb. ^{227}Th can be obtained from ^{235}U stocks or from ^{226}Ra via neutron activation through the decay of ^{227}Ra to ^{227}Ac (half-life: 22.7 y) which can be loaded in a generator for production of ^{227}Th. Finally ^{149}Tb can be produced by a spallation reaction at a high energy (1400 MeV), again with non-trivial mass separation. It is at the moment produced at CERN and its use limited to preclinical studies.

For a pharmaceutical company interested in the develop-

ment of alpha-emitter therapy the choice of the most appropriate radionuclide is not easy and should take into consideration advantages and drawbacks for each radionuclide (Table 1).

Table 1. Advantages and drawbacks of clinically potential alpha-emitting radionuclides.

Alpha-emitting radionuclides	Advantages	Drawbacks
Bismuth-213	reasonably easy production, daily availability, well established chemistry moderate cost	short half-life (45.6 m) waste associated to production
Actinium-225	potential availability, well established chemistry, appropriate half-life (10d), moderate cost Nanogenerator concept	difficult production (requires radioactive Ra-226 target or high energy accelerator) potential contamination of Ac227 waste associated to production, need for internalization
Astatine-211	Mature production scheme potential availability appropriate half-life (7.2h), moderate cost	waste associated to production difficult chemistry no internalization possible yet
Lead-212	well established production daily availability, established chemistry appropriate half-life (10.6h),	waste associated to production, high cost, limited number of producers
Thorium-227	accessible production	production limited availability, longhalf-life (18.7 d) high cost waste
Terbium-149	• easy chemistry •very high purity,	limited production capability potential availability, short half-life (4.1 h), limited number of producers

Combination Radionuclide therapy/ Immunotherapy

Ionizing radiation has been proven to stimulate the immune system in multiple ways [32]. Consequently radiotherapy, and especially targeted radiotherapy, has a significant immunomodulatory effect. Targeted radiation can increase tumor immunogenicity through the induction of several tumor cell death forms and the release of pro-inflammatory cytokines and chemokines. It has been known to induce systemic immune-mediated anti-tumorigenic effects known as abscopal effect [33,34].

Prostate malignant tumors are often infiltrated by inflammatory cells suggesting a host immune response which can be thwarted by several factors and mechanisms. The result is the inhibition of antitumor immunity by activation of negative regulatory checkpoints [35]. For the last 10 years several clinical trials were conducted using different classes of immune modulators and the first therapeutic vaccine, sipuleucel-T (Provenge®, Dendreon, Seattle, USA) was approved by the FDA for patients with minimally symptomatic metastatic prostate cancer. This vaccine targets the immune response toward the defined prostate antigen PAP (Prostatic Acid Phosphatase). A median gain survival of 4.1 months over placebo was observed in a phase III trial (IMPACT) [36]. A phase II randomized clinical trial combining Sipuleucel-T with ^{223}Ra (Xofigo®) vs Sipuleucel-T alone is recruiting (NCT02463799) for a planned total number of patients of 34 and a completion date in 2020.

Another vaccine, PSA-TRICOM (PROSTVAC) designed to induce activation of T cells specific against prostate-specific antigen (PSA) was used in a phase II trial showing a significantly prolonged median overall survival combined and further in a phase III trial which has been completed. It was combined with 153Sm-EDTMP (Quadramet®) in a randomized phase II trial in patients with metastatic castration-resistant prostate cancer without visceral metastases. Interestingly a significant increase in PFS was found with evidence of serum PSA decline only in the combination arm [37]. This was the first clinical trial combining a radiopharmaceutical agent with a immunotherapy modality. Over a dozen phase II and phase III clinical trials combining immunotherapy and radiotherapy (mainly external beam radiotherapy) have been completed or are in-progress, demonstrative of the momentum this concept has [38].

Programmed Cell Death (PD-1) inhibitors have delivered impressive anti-tumor efficacy in some solid tumors (melanoma, non-small cell lung cancer and renal cell cancer) but seem less promising in prostate cancer. Indeed no objective response was observed in 17 patients with castration-resistant prostate cancer who were treated with pembrolizumab, a humanized anti-PD1 antibody in phase I study [39]. This relative failure was related to the paucity of PD-L1 staining in prostate cancer tissue specimens [17]. In this study only 15% of samples showed focal areas of PD-L1 positivity. Moreover some correlation was found between expression of PD-L1 and response to PD-L1 blockade [39]. Immunohistochemical analysis in tumor specimens of 42 patients showed no objective response to anti-PD1 antibody treatment in 17 patients with PD-L1 negative tumors whereas 9 of 15 patients (36%) with PD-L1 positive tumors had an objective response.

Despite this paucity of PD-L1 expression in prostate cancer it is possible to upregulate it by tumor cell extrinsic signals including androgen deprivation and radiation therapy [38]. A recent clinical study showed, for the first time, evidence for meaningful and clinical activity for PD-1 blockade in patients with metastatic castration-resistant prostate cancer and who were resistant to enzatulamide treatment [18]. Three patients of the 10 enrolled demonstrated surprising and unexpected antitumor activity. Indeed starting from PSA serum levels of 46, 71 and 2,503 ng/ml, a near complete biochemical response was observed reaching a serum PSA level of ≤0.1 ng/ml. Two of these three patients had a partial response in liver mets with discontinuation of opiate analgesics and resolution of pain. These results tend to show that androgen-deprivation may augment an anti-tumor immune response and provide, for the first time, evidence for meaningful clinical activity for PD-1 blockade in men with metastatic castration-resistant prostate cancer

The Future - Commercial Success

Many of the themes in this article have direct impact on the potential for commercial success. Without effective and widely available products making a difference to patients, the field has a limited future, despite current momentum. There are three main considerations that will largely determine the future of theranostic nuclear medicine.

The first consideration relates to clinical trials. As discussed repeatedly in this article, there are very few robust examples of prospective, controlled and statistically-meaningful clinical trials to demonstrate efficacy. This is not just the case for therapeutic products but also imaging. In some territories, NET and PSMA imaging have been relatively well adopted without much robust clinical evidence. In this context it's not just the clinical utility that matters, it's also the evidence required to deliver reasonable reimbursement. Without payors, adoption will be limited, particularly in the United States and Europe.

However, it will not be enough to simply run clinical trials. The second major issue is that nuclear medicine trials – again both diagnostic and therapeutic – need to be run in conjunction with standard care. While it may be tempting to start with salvage patients, there is ample reason to at least consider combination trials with end-life chemotherapy, especially given the fact that many anti-neoplastic agents confer a radiosensitization benefit. Such trials take longer and are more expensive but are ultimately required for the field to progress because of their engagement with mainstream medical oncology. Radiopharmaceutical trials in combination with hormone therapy and immunotherapies are also going to be increasingly important, particularly in solid tumours, where the proportion of responding patients in many cancer setting is still relatively small.

Finally, a robust supply chain will be critical-both for ^{177}Lu and alphas. There are a growing number of companies that are able to offer commercially useful quantities of radionuclides, although multiple scaled-up vendors are going to be ultimately needed for "big pharma" companies to believe in the potential of routine use of radiotherapeutics, not just to guarantee availability but also redundancy of supply. The complexity and "just in time" nature of radiopharmaceutical manufacturing means that it is vital that oncologist – and patients – have confidence.

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