Journal of Nuclear Medicine, published on November 17, 2016 as doi:10.2967/jnumed.116.184994

From NETTER to PETTER: PSMA targeted radioligand therapy

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In this month's issue of *The Journal of Nuclear Medicine*, Rahbar et al present exciting retrospective German multicenter data (12 centers) on the performance of PSMA targeted radioligand therapy (RLT) using ^{177}Lu-PSMA 617 in metastatic castration resistant prostate cancer (mCRPC). The authors describe in detail the safety and efficacy of this new theranostic approach applied under the “compassionate use” provision in 145 patients.

It took 20 years for somatostatin receptor directed radioligand therapy (also commonly abbreviated as PRRT for peptide receptor radioligand therapy) to get close to EMA and FDA approval (as of today still pending). However, PSMA-directed therapy seems to be off to a very promising start. The high demand for PSMA-directed radioligand therapy started with the initial report by Zechmann et al. who described the use of a ^{131}I-labelled PSMA-ligand (*1*). After the subsequent introduction of theranostic agents both for imaging and therapy (e.g. PSMA 617, PSMA I&T) multiple centers in Germany and worldwide (e.g. Australia, Turkey and India) adopted this treatment option predominantly using ^{177}Lu as therapeutic nuclide. Initial clinical experience was followed by multiple relatively small single institution studies reporting on initial clinical experience with ^{177}Lu-PSMA RLT (*2-7*). However, these studies included a wide range of patients with varying initial and subsequent treatments, different disease stages and variable study endpoints.

Rahbar's report is the result of a multicenter initiative headed by the German Society of Nuclear Medicine (DGN) that attempts to accelerate the clinical adoption of PSMA targeted radioligand therapy (*8*). This initiative is highly relevant for patients with advanced disease and is also important for the future of nuclear medicine. Future success will of course depend on a NETTER trial like prospective study that paved the way for somatostatin receptor targeted theranostics.

Authors of the DGN consortium summarize experience with 248 treatment cycles in 145 patients. The results are impressive. A ≥50% decline in PSA-levels occurred in 45% (45/99) of patients in whom follow-up on PSA-values were available. These data are in line with previous smaller studies – some of which are also part of the current report (as described under supplemental data). Remarkably, the primary endpoint of a ≥50% decline in serum PSA levels was achieved already after the first cycle in >90% of responding patients (40 out of 45). Thus, early identification of non-responders is feasible allowing for early treatment adaptations in non-responding patients. In addition, first exploratory data are presented discussing potential negative (visceral metastases, high alkaline phosphatase) and positive (number of cycles applied) response predictors.

The last few years saw the emergence of five new drugs for mCRPC. (Abiraterone, Enzalutamide, Sipuleucel-T, Cabazitaxel, and ^{223}Ra) that resulted in some survival benefits (*9-13*). Rahbar' data suggest that benefits comparable to those achieved by pharmacologic approaches can be matched or exceeded with ^{177}Lu-PSMA RLT. Thus, it could have a major impact on the management of patients with mCRPC. However, larger prospective randomized trials with endpoints including progression free and overall survival will be needed to determine the precise role among the other emerging therapeutic options.

Given the apparent high efficacy in this heavily pre-treated patient group with advanced disease, ^{177}Lu-PSMA RLT appears to be very well-tolerated. Grade 3-4 very manageable hematologic toxicity occurred in 12% of the patients (4% thrombocytopenia, 10% anemia). This is comparable to other treatment approaches in advanced mCRPC. A comparable rate of hematologic toxicity was reported in the ALSYMPCA trial (^{223}Ra-dichloride) (*11*). Moreover,

second line chemotherapy or radiolabelled antibody therapy is clearly associated with higher rates of toxicity (*12,14*).

In summary, these German multicenter effort provided promising preliminary data on effectiveness and tolerability of PSMA targeted RLT in mCRPC. Our communities (urology, nuclear medicine) are now challenged to avoid the slow translation and acceptance of somatostatin receptor targeted PRRT. In Germany, this therapy is still applied under compassionate use. Only the very recent NETTER-1 trial data have apparently succeeded in finally getting close to market approval and reimbursement in Europe, the US and other parts of the world. A **PETTER** (**P**rostat**E** cancer **T**reatment using endoradio**T**h**ER**apy) trial appears to be the most appropriate response to this challenge. Prospective multicenter randomized trials proving the clinical efficacy of ^{177}Lu-PSMA RLT heading towards approval and reimbursement are now needed urgently. This is even more challenging as the field of Nuclear Medicine has struggled in the past quite substantially conducting multicenter trials. On a more optimistic note, our discipline may translate the lessons learnt in the past and hopefully capitalizes on the knowledge of our clinical partners which we attempt to summarize as follows:

1. NETTER-1 used available data from clinical experience to initiate a phase 3 study. With regards to ^{177}Lu-PSMA this should help with defining treatment doses and minimize dosimetry requirements. As learnt from NETTER-1, a priori discussions with the regulatory agencies should be very helpful.
2. The ALSYMPCA trial taught that overall survival, pain assessment and skeletal events are important endpoints in the management of mCRPC patients facilitating approval and reimbursement. However, as various treatment options are available it would be unethical to compare ^{177}Lu-PSMA RLT to best supportive care or even placebo. The practical way for study approval and successful enrolment of patients is probably the randomization into two groups both getting medical treatment (e.g. enzalutamide or abiraterone) with one group receiving additional ^{177}Lu-PSMA RLT. This combination treatment might even enhance the efficacy of ^{177}Lu-PSMA as there is a potential upregulation of PSMA-expression under hormone ablation (*15*).

3. Definition of appropriate clinical endpoints need to be defined in accordance with the recently updated prostate cancer working group (PCWG) 3 framework (*16*). Despite its well-known limitations the PSA-response after 12 weeks remains the key measurement for short-term outcome in all major recent studies. As much as the nuclear medicine community likes to assess the treatment response using theranostic tools (e.g. PSMA-PET for treatment monitoring of ^{177}Lu-PSMA RLT) these methods have not been validated and are thus not yet been established as objective response parameters. Therefore trial designs need to employ CT and bone scintigraphy criteria which in prostate cancer are clearly accepted as outcome measurements for progression-free-survival (PFS). These trials could then be used to add follow-up diagnostic PSMA studies to validate the PET approach as an intermediate endpoint biomarker.

In summary, ^{177}Lu-PSMA RLT has the potential to develop into a powerful treatment in mCRPC patients. Its precise position within the growing portfolio of treatment options will need to be established prospectively in well-designed multicenter studies.

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