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177Lutetium-PSMA in Advanced Prostate Cancer

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Abstract

The high incidence rates of prostate cancer increase the need for improved therapeutic strategies. Second to skin cancer, prostate cancer is the most common neoplastic injury in North American men. Over a lifetime, 1 out of 7 men will receive a diagnosis of prostate cancer. Although most patients present with localized or indolent disease, there are still a big proportion of patients that will eventually progress to metastatic prostate cancer, for which no curative treatment currently exists.

Keywords: Advanced Prostate Cancer; mCRPC, 177Lutetium; PSMA (Prostate-Specific Membrane Antigen); Serum Prostate Specific Antigen (PSA); Benefit/Risk Assessment; mCRPC; Clinical Practice

Introduction

Prostate tumors specifically express the prostate-specific membrane antigen (PSMA), a membrane-bound protease that is largely overexpressed in malignant prostate tumor cells and its expression rate correlates with the aggressiveness of the disease [1-3]. In fact, recent published studies have proposed the possibility of targeted radionuclide therapies such as 177Lutetium-PSMA as a therapeutic option in men with advanced prostate cancer [4-9]. In this letter to the editor, with the use of a case report, I will summarize some of the main components associated with targeted radionuclide therapies such as 177Lutetium-PSMA in order to be able to answer questions raised by many patients and clinicians dealing with patients suffering from advanced prostate cancer where treatment options become limited. Obviously, in the context of this letter limited aspects of this new therapy will be discussed.

Case Report

A 68-year-old patient known for an undifferentiated and an invasive stage IV prostate cancer with a Gleason score of (5+4 = 9/10) came to your office for counselling. He was treated with Zoladex and Casodex for 3 years. Due to the resistance to Casodex, the patient was put on Zytiga, a second line hormone therapy in combination with Zoladex and prednisone. The patient is also known for bone metastasis for which he received Xgeva once a month. Since he is not highly interested by chemotherapy, he wants to know what the best treatment approach for him should be considering that gene therapy; immunotherapy and Nano therapy treatment modalities will most likely not be available before the next 3 to 5 years. Therefore, he is still concerned about what treatment would be available once he will no longer be responsive to this second-line hormone therapy. It is known from many years that PSMA is a 750 amino acid type II transmembrane glycoprotein receptor plays a role in cell migration, cell survival and proliferation [10]. Wright GL et al. [11] have demonstrated that while PSMA is expressed at low levels in normal human prostate epithelium, it is overexpressed (up to 1000 times higher than in normal prostate cells) in almost all prostate cancers. Authors have also shown that 5-10% of prostate cancers appear not to express the PSMA glycoprotein; these cancers have been defined as being receptor-negative which means that treatment using PMSA receptor will not be a good choice for the patients with advanced prostate cancer. Wright GL et al. [11] have also observed that the density of expression of this transmembrane receptor on prostate cancer cells further increases dependent on the Gleason score of the prostate cancer, and in hormone-resistant prostate cancers [11]. Considering that our patient has a Gleason score of 9 and bone metastasis from the time of diagnosis this makes him an ideal candidate for this radionuclide therapy. Among the following items, which one(s) is/are considered the main elements involved in the comprehension of Lu177-PSMA therapy that you should discuss with your patient. Considering the context of this letter I will only discuss some of the main elements.

a) PSMA is not Entirely Prostate Specific

As mentioned in a clinical review by Emmett L et al. [12] PSMA is not entirely prostate specific and is expressed in other

cells including the small intestine, proximal renal tubules and salivary glands [12]. Although the expression of PSMA on these cells is significantly reduced when compared to prostate cancer cells, there is a radiation dose that can be delivered to these target organs when PSMA is used as a target for radionuclide therapy [12]. This has an impact on the benefit/risk profile of PSMA-targeted therapy, and on the determination of the safe dose of radiotherapy that can be delivered to the patient with advanced prostate cancer without causing significant radiation damage to non-target organs. In clinical trials to date, the organs that have been identified as most at risk from PSMA-targeted therapy are the salivary and the lacrimal glands [12]. Clear cell renal cancer has also been reported to express the PSMA receptor, and there are case reports of the use of PSMA as a staging tool for renal cancer [13,14]. Other cancers may also be visible on PSMA diagnostic imaging, but the cells do not overexpress the PSMA receptor on the cell surface. This is an important consideration for our patient as it is possible that PSMA-targeted therapy will be affecting other tissues that are positive for PMSA receptors especially the kidney and the intestine. In fact, patients with mild or moderate renal impairment may be at greater risk of toxicity. Therefore, it is suggested to perform more frequent assessments of renal function in patients with mild to moderate renal impairment as well as to provide a close monitoring of the adverse events related to the digestive system. On the other hand, our patient has normal renal and intestinal functions which further reduce the risks for renal toxicity. But, as always, a close monitoring is still required for the other adverse drug reactions that might be associated with this health product. Therefore, A is a good answer.

b) 177Lutetium (177Lu) Characteristics

As mentioned by Emmett L et al. [12], 177Lutetium (177Lu) has gained popularity as the therapeutic radionuclide of choice due to its desirable physical properties [12]. It is suitable that, the emission characteristics of a therapeutic radionuclide should match the lesion size/ volume to be treated to mainly focus energy within the tumor rather than in the tissue surrounding the lesion [12]. Unfortunately, our patient has many bone metastases with a very small nodule on the prostate which might reduce the benefits of this therapeutic approach. Fortunately, 177Lu is a medium-energy β-emitter (490 keV) with a maximum energy of 0.5 MeV and a maximal tissue penetration of <2mm. As explained by Emmett L et al. [12], the shorter β-range of 177Lu provides better irradiation of small tumors, in contrast to the longer β-range (12), which turns to be recommendable for our patient. The γ-emission from 177Lu allows for ex vivo imaging and consequently the collection of information pertaining to tumor localization and size which will be helpful for the follow-up of 177Lu therapy. Furthermore, these authors added that 177Lu has a relatively long physical half-life of 6.73 days which allows for the delivery of high activities of 177Lu PSMA to prostate cancer cells [12]. Currently there are no long-term prospective Randomized Controlled Trials (RCTs) available for the evaluation of PSMA-targeted radioligand therapy on survival benefits compared with approved standard therapies for advanced prostate cancer such as abiraterone, enzalutamide, radium-223-dichloride, docetaxel or cabazitaxel. Randomized controlled trials are now underway to elucidate whether PSMA used for diagnostics and treatment of prostate cancer can postpone the progression to death and reduce mortality. Therefore, B is a correct answer.

c) Labelling of Lu 177 with PSMA Peptides: Different Available Options

There are a number of different PSMA peptides and antibodies [12,15] that have been labelled with 177Lu, and which have been utilized in both clinical trials and for clinical use as therapeutic agents in men with metastatic castration resistant prostate cancer (mCRPC) [12,16]. The compound PSMA-DKFZ-617, has frequently been discussed in the medical literature but clinically significant data are still pending in humans. This is a small molecule peptide, rather than an antibody, chemically conjugated with 177Lutetium. In an initial study in mice, a highly efficient internalization into prostate cancer cells was observed with approximately 75% of the peptide bound to the cell internalized after 3h of incubation indicated Emmett L et al. [12] in their literature review [12]. A similar small molecule PSMA peptide ending with a different chemical conjugation (177Lu PSMA-I&T) also appears effective as a therapeutic agent in a number of published studies summarizes by Emmett L et al. [12]. 177Lu PSMA is an easily administered targeted therapy with no significant symptoms at the time of injection. As mentioned by Emmett L, et al. [12], the main safety issues are standard radiation safety precautions that are inherent in all intravenously injected, renal excreted radionuclide therapies [12]. Obviously, this product seems promising, however, this product has not been authorized for the treatment of advanced prostate cancer in any countries, at this time. Certainly, this product can be available via the participation in clinical trials, where necessary, or via the Special Access Programme (SAP) for having access to drugs that are unavailable for sale in Canada for treating patients with serious or life-threatening conditions when conventional treatments have failed, are unsuitable or unavailable. Therefore, C is a good answer.

d) Treatment Efficacy

In the TROPIC, phase III clinical trial, the number of men who experience a >50% reduction in serum PSA levels ranges from 30% to 70%, which is highly comparable to the PSA response rates achieved by chemotherapy agents used in mCRPC (Cabazitaxel and Docetaxel) [17]. Those men with progressive disease who do not respond to 177Lu PSMA therapy range from 10% to 32% which is a source for concerns for our patient. One of the larger studies, performed by Baum RP et al (2016) which included 56 men; 80% of all men had a positive PSA response to therapy [6] which is re-assuring for our patient due to this treatment efficacy. All currently published studies revised by

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Emmett L et al. [12], 177Lu PSMA therapy in prostate cancer are retrospective, mostly single arm, and involve a variety of treatment regimens, both in terms of dose given (ranging from 3.5 to 8.0 Gbq/injection of Lu PSMA) and the number of doses administered (ranges from a single injection up to 4-6 injections 6 weeks apart) [12]. This retrospective study makes interpretation of the efficacy of 177Lu PSMA treatment difficult at this stage and without an accurate efficacy assessment; it is difficult to recommend this therapeutic approach to our patient but could be considered in men with mCRPC who have extinguished all other treatment alternatives [12]. The next step needs to get prospective RCTs testing the efficacy of 177Lu PSMA in trials that are powered enough to assess overall survival, randomized against treatments already shown to have a survival benefit (appropriate comparator such as Zytiga or Jevtana for example). Due to the retrospective and single arm treatment nature of currently published trials there is little information on a possible survival benefit of Lu PSMA therapy in men with mCRPC [12]. A study performed by Baum RP et al. [6] in 56 patients receiving up to five treatments of Lu PSMA at 6-weekly intervals appeared to suggest that there may be a survival benefit. This study found that with a follow-up period of 28 months, 12 patients died (21.4%). Survival after 28 months was 78.6%. Median progression-free survival was 13.7 months [6] Once again prospective RCTs will need to confirm any potential survival benefit due to 177Lu PSMA in men with advanced prostate cancer using 177Lu PSMA against an authorized comparator. Again, before recommending this therapy to our patient we need prospective RCTs long enough and with an appropriate number of patients to permit an acceptable benefit/risk assessment. Therefore, D is a correct answer.

e) Predictors of Response

Not all men with mCRPC will have a good treatment response to 177Lu PSMA. In the literature review made by Emmett et al. [12], up to a 33 percent of those men treated to date show progressive disease despite treatment which is an important source of concern for our patient. This is likely due to a variety of factors. One important factor is whether or not the tumor cells uniformly express a high density of the PSMA receptor in the targeted tissue. Because heterogeneity of PSMA receptor activity within the tumor population may mean that some sites will not respond to treatment with 177Lu PSMA, which will manifest as disease progression, and in a rising of the PSA [12]. Currently PSMA activity is measured by assessing intensity of activity on a 68Ga-PSMA staging PET/CT and is a requirement for treatment in all currently published studies [12]. A recent study done by Ferdinandus J et al. [18] in 40 patients identified platelet level and the need for pain relief as the most significant predictor of poor response to 177LuPSMA, likely reflective of the burden of metastatic bone disease [18]. This same study did not find that intensity of PSMA activity on 68Ga-PSMA staging PET/CT was predictive of response [18]. Other studies have commented that bone metastases appear to respond less well than visceral or lymph nodal disease to treatment with 177Lu PSMA [6] which is also a source for concern in our patient presenting with many bone metastasis but no liver metastasis. Again, we do not have enough prospective information to perform an acceptable benefit/risk assessment and until further long-term prospective RCT studies become available, we cannot recommend this therapeutic approach except in certain circumstances on a case by case basis. Therefore, E is a good answer.

f) Toxicity

As summarized in the literature review by Emmett et al. [12], overall, toxicities related to 177Lu PSMA therapy have been of low grade and manageable with close monitoring. Up to 30% of men report dry mouth or xerostomia following treatment. Fatigue is a common side effect in up to 25% of men treated [12]. Nausea can also be significant and has been reported in up to 10% of men, particularly in the 24-48 h after the injection. None of the current studies have reported renal toxicity although it is likely that this will be a longer-term complication therefore a close monitoring is recommended. Hematological toxicity is the most commonly reported serious side effect related to 177Lu PSMA therapy that also deserves a close monitoring and the follow-up of local specific clinical practices guidelines. This is predominately an innocent bystander effect in men with a heavy burden of skeletal metastases and borderline marrow function, rather than a direct radiation effect on bone marrow. In men with significant bone metastases, up to 10-25% of men had a Grade 1-2 reduction in hemoglobin or platelets that should be clinically manageable [12]. No significant marrow toxicity is seen in those men who do not have a high burden of bone metastases. Because of the longer particle range of 177Lu, compared to alpha emitters such as radium 223, it is likely that 177Lu will have a higher radiation dose to surrounding marrow in men with extensive metastatic bone disease, than alpha emitter treatment options. Initial studies using 225 AC (actinium) PSMA-617 have confirmed this relative sparing of bone marrow in men with extensive bone metastases using a PSMA labelled alpha emitter [19]. As always, the adverse drug reactions are an important source for concerns for mCRPC patients. That is why we recommend this treatment only if the benefits outweighing the risks. Therefore, F is a correct answer.

Conclusion

Considering that our patient has bone metastasis and a low PSA level, a question still remains at that time: is Xofigo a better choice for our patient? Xofigo® (radium Ra-223 dichoride) has been the main treatment option of mCRPC since few years. Not only does it provide significant pain palliation and reduce skeletal-related adverse events, it also slows down progression of the disease, increasing median survival by about 30 percent [20]. As discussed, many recent studies have looked at a potentially important new form of radiotherapy called lutetium-177 (Lu-177). Lu-177 is a low-energy β-particle emitter which is a good thing because it limits the distance β-particles can travel

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through tissue [12]. Ideally, for our patients we want internal radiotherapies to deposit their energy in tumor tissue only; radio-emitters that deposit their energy over long distances are too toxic for internal therapeutic applications [12]. Xofigo is an α-particle emitter; α-Particles are very heavy and can travel only a short distance through tissue; however, they deposit a lot of energy in the tissue they interact with, efficiently killing cancer cells in a small radius [20]. Because β-particles such as Lu-177 are thousands of times smaller than α-particles, they can travel farther through tissue, but their cell-killing power is less [12]. Another desirable quality in radiotherapeutics is a half-life that should be long enough to allow for convenient treatment and time in the body to kill off cancer cells. But, it should also be short enough in order to not staying too long in the circulation, accumulate in the liver and kidneys, and kill healthy tissue as mentioned by Emmett L et al. [12]. Both Ra-223 and Lu-177 have that criterion. Ra-223 is chemically similar to calcium, so tissues that uptake calcium uptake radium as well principally in highly metabolically active sites likes bone metastases. However, calcium is found everywhere in the human body; therefore, small amounts of radium may accumulate in other tissues, causing various toxicities. Lu-177 by itself has little therapeutic use; however, when attached to an antibody found (PMSA) on the surface of at least 95 percent of prostate cancer cells it becomes more efficient. Unlike Xofigo, which only attaches to bone metastases, Lu-177-anti-PSMA attaches to any metastasis including bone, lymph node or visceral metastasis. It can potentially treat systemic micrometastases as well. Consequently, Lu-177-anti-PSMA has the potential ability to kill many more cells because of the increased range of the β-particle. Lu-177 has another important benefit over Ra-223: it emits small amounts of highly penetrating γ-rays. Interestingly, the γ-rays are not powerful enough to kill tissue, but they can be detected by a 2D γ-ray camera (scintigraphy), or a 3D SPECT scan. This means that we can see even small metastases that the radiotherapy is attacking. Therefore, Lu-177-anti-PSMA is both therapeutic and diagnostic. Tagawa ST et al. [21] published the results of a Phase II clinical trial that demonstrated Lu-177-anti-PSMA resulted in declines in PSA among patients with mCRPC. In a follow-up analysis, they reported a better response, including increased survival, but with higher toxicity with increased dose [21]. They also noted large declines in circulating tumor cells (CTCs) which is in important biomarkers for the follow-up treatment of advanced prostate cancer [22]. Therefore, both molecules are acceptable for our patient but with Lu-177-anti-PSMA we do not have enough background information (enough prospective RCT studies) at this time to recommend Lu-177-anti-PSMA over Xofigo. Also, we do not have face to face studies comparing directly Xofigo to Lu-177-anti-PSMA to better determine which one is the most recommended by performing superiority or non-inferiority analysis. LUTATHERA (lutetium Lu 177 dotatate) is a radiolabeled somatostatin analog has been authorized by the FDA in January 2018 for the treatment of somatostatin receptor-positive gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults [23]. This is encouraging for our patient considering this new marketed drug and by the fact that Lutetium 177 (Lu) labelled PSMA peptides is progressing well in its clinical development. Even with considering the above concerns, we can be optimistic that this treatment will become authorized soon for patients suffering from mCRPC. Then as we get more and more data, we will most probably be able to perform an appropriate benefit/risk assessment and determine survival data. Currently there are no prospective RCTs available for the evaluation of PSMA-targeted radioligand therapy and to determine the survival benefit over approved standard therapies such as abiraterone, enzalutamide, radium-223-dichloride, docetaxel or cabazitaxel. 177Lu-PSMA-targeted radioligand therapy should therefore currently only be offered after critical evaluation in patients who exhausted the approved standard therapies [16].

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