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NUCLEAR MEDICINE IN PROSTATE CANCER RELAPSE AND BIOCHEMICAL RECURRENCE

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Abstract

Prostate cancer (PCa) provides different types of approach, both as regards the diagnostic and therapeutic aspects, based on the stage of disease. Nowadays, multi-parametric MRI (mpMRI) plays a pivotal role in primary prostate cancer diagnosis and opens the door to the planning of therapeutic st In this fields, conventional morphological imaging showed limited accuracy for assessment of biochemical recurrent prostate cancer (BRPCa), advanced disease and post-therapy monitoring and evaluations.

Nuclear medicine has a metabolic or receptor point of view that is often helpful in situations where morphological analysis is not enough. Radiolabeled choline (11C or 18F), base its use on the exalted neoplastic cell membranes turnover and phosphatidylcholine production increase.

Thanks to its features, 68Ga-PSMA PET imaging is affirming in entire PCa diagnostic scenario: from local recurrence and advanced disease to primary tumor localization and lymph nodes disease detection; up to the most future-oriented applications that include radio guided surgery (RGS) and theranostics with 177Lu-PSMA. Having achieved excellent levels of diagnostic accuracy does not stop nuclear medicine research which for these comparison scenarios today also proposes the use of 11C-acetate and 18-Fluciclovine that undermine choline PET/CT and PSMA PET/CT results, in a race for the best possible diagnostic performance.

Nuclear medicine is also very active in the study of "bone scenario", it represent an essential evaluation for correct defining the disease stage. As for diagnostics, also in the therapy's field we observe the flowering of new solutions, to try to improve both the survival and the quality of life of the patient: 223Ra-dichloride and 177Lu-PSMA are two of the most brilliant examples. Finally, the look towards the future cannot ignore the advent of hybrid systems; from this point of view the diamond shining in the near future undoubtedly seems to be PET/MRI, fixing the maximum anatomical definition with finest metabolic-receptor informations.

Keywords: *Prostate cancer; Relapse; Recurrence; CT/PET; Bone scan; 68Ga-PSMA PET; 18F-Na PET; 223Ra; 177Lu*

Introduction

Prostate cancer is a common malignancy leading to substantial morbidity and mortality.
To date, the diagnostic path for primary disease is very solid. The guide for the histological definition through biopsy and the study of the local extension of the disease is excellently carried out by methods that involve MRI more and more.

Furthermore, thanks to mpMRI and with the use of dedicated sequences (T2-weighted imaging, diffusion weighted imaging, dynamic contrast-enhanced imaging, MR spectroscopy) it is possible to characterize the lesions even more precisely.

LIMITATIONS OF TRADITIONAL IMAGING

After primary treatment with surgery or radiation therapy, many patients present biochemical relapse of disease with evidence in serum of rising prostate-specific antigen (PSA).
This biochemical recurrence often precedes any symptoms.
In this scenario, diagnostic imaging methods must be able to detect the site of tumour relapse and to evaluate the tumour extent. Unfortunately, conventional morphological imaging showed limited accuracy for assessment of biochemical recurrent prostate cancer (BRPCa); and also for advanced disease and post-therapy monitoring and evaluations.

Several studies show some limitations not only in traditional imaging fiels, but also about one of the cornerstones of nuclear medicine: 18F-FDG PET/CT. Generally, 18F-FDG is able to detect cancer due to increased expression of cellular membrane glucose transporyer 1 (GLUT-1) and enhanced hexokunase II enzyme activity in tumor cells. The Warbur effect, consisting of an increased glycolytic pathway in cancer cells explains the wide utilization of this kind of radiotracer as imaging biomarker in oncology.

In PCa the utility of 18FDG is related to the tumor differentiation: GLUT-1 expression is higher in poor differentiated variants and not remarkable in well differentiated hormone-sensitive ones. (1)

Specified this, primary cancer detection 18F-FDG PET/CT has a relatively low sensitivity. Two of the tracer's biggest weaknesses are: physiological excretion through urinary tract, with a negative impact on the visualization of pelvic area and the FDG uptake also in normal prostatic gland or benign prostatic hyperplasia (BPH). (2)
In conclusion, 18F-FDG PET/CT is useful for detection of aggressive disease, treatment efficacy evaluation in metastatic disease and prognostication in patients with castration resistant variants of PCa. (3)

Due to all these reasons, it's a very good new the recent massive development of metabolic imaging methods and novel PET radiopharmaceuticals, improving the diagnosis advanced disease and BRPCa, even when serum PSA levels are very low.

PET RADIOFARMACEUTICALS IN PCa

11C and 18F- choline

About two decades ago, Hara et al. described 11C-choline and 18F-choline (FCH) as the most promising PET agent for evaluation of PCa. (4)
Choline is a quaternary ammonium base, it works as an important component of phospholipids and cells membrane in all living organism. As concerning its metabolism, choline is present in three major pathways: phosphorylation, oxidation and acetylation. (5)

The principal premise to its diagnostic imaging use is an increase uptake in malignant cells, due to up-regulation of choline kinases; as result of this metabolic change , we can observe an enhanced production of phosphatidylcholine, incorporated in tumor cell membranes (6)
This context shows a deep connection between oncogenic signalling and choline metabolism. This fact also reflect the evidence of a different cell membrane fatty acid composition, between normal and malignant cell. (7)
Remarkble is the strong link between choline and aerobic metabolism, confirmed by low or absent

uptake under hipoxia: a hallmark of cancers that exibit anarchist neo-angiogenesis. (8)

In the field of tracers that use choline there is a head to head especially between 11C and 18F-choline, advantages and drawbacks are inverse. (9)
11C-Choline guarantees a better visualization of the pelvis due to its low urine excretion, if imaged early (half life 20 minutes); 18F-Choline has higher urinary excretion, influencing image interpretation of the pelvis but it has a longer half life and as opposed to 11-Choline it doesn't need cyclotrone. (10)

Appropriateness of PET/CT using radiolabeled choline for PCa diagnosis has been evaluated in some investigations, suggesting a not ideal profile in primary disease.
Conversely, in biochemical failure and restaging 11C-Choline PET/CT has an important role in the assestment fo lymph node metastasis and disease extension, with a sensitivity linked to PSA levels in serum (11-12); some groups described a similar detection rate of relaps site in patients with rising PSA also using 18F-Choline. (13)
Several studies also reported good performances of 11C-Choline PET/CT in scouting of bone metastases (14). Recently it has been suggested a 11C-Choline role for monitoring metastasis-directed or systemic therapies. (15)
In this interesting and wide scenario, twisted with therapy's strategy, Choline-PET has shown the potential to change the therapeutic approach also for radiation oncologist.
Even if many reliable data seem to be promising, the current role of radiolabeled Choline PET/CT in irradiation treatment planning still remains under investigation. (16)

Unfortunately, choline PET suffers from limited sensitivity in detecting disease at low PSA levels. These limitations, in turn, have led to the search for newer PET tracers and imaging biomarkers to help increase sensitivity and accuracy of imaging in PCa detection.

PSMA family

The prostate specific membrane agent (PSMA) is a type II transmembrane glycoproteine, physiologically express in many tissue types and significantly up-regulated in PCa, thanks to this feature it represent a very helpful target to increases diagnostic accuracy in detecting and guiding management in various stages of the disease pathway.
In prostate cancer PSMA overexpression is observed, it explain the greater sensitivity of radiolabeled agents targeting this protein in tumour detection.
It' important to note that also other kind of neoplasms, including renal, bladder, breast, and colon cancer, show PSMA expression expecially in neovascularity's areas.

When used as a target for PET imaging with Gallium 68 (68Ga) labelling, physiological distribution includes a relatively intense uptake in salivary glandsand kidneys;
a moderate activity is observed in lacrimal glands, liver, spleen, and intestines.
Excretion of unbound tracer occurs via the urinary tract. (17)

68Ga-PSMA is produced using a 68Germanium(Ge) / 68Ga radionuclide generator.

Thanks to its features, 68Ga-PSMA PET imaging is affirming in entire PCa diagnostic scenario: from local recurrence and advanced disease to primary tumor localization and lymph nodes disease detection.

A risk of biochemical recurrence is possible for PCa patients who have had radical prostatectomy or radiotherapy, principal marker of this kind of situation is a rising PSA in serum.
Detection of recurrence in the prostate or in the surgery bed at low PSA levels is certainly challenging, always for nuclear medicine; for example choline PET tracers have a detection rate ranging from 19% to 36% when serum PSA is below 1.5 ng/ml.
There is evidence, when compared with choline PET, that PSMA result to be superior in investigations of recurrence at prostate, surgery bed, limph nodes and skeletal level.
In addition to PSA serum levels, PSMA PET is also positively correlated with the Gleason Score: there are some evidences in some studies that higher

Gleason grade tumours express more PSMA receptors and this fact explain how higher Gleason score result correlated with positive PSMA PET imaging.

In advanced disease PSMA PET play an interesting role, mainly because it can be suitable to assess response to treatment and also to guide radionuclide therapy.
But one of the unequivocal great news linked to PSMA PET lies in its ability to impact primary staging, until a few years ago the exclusive field of radiology with MRI and mpMRI. Recently, 68Ga-PSMA has been evacuate in simultaneous PET and MRI scanners and there is evidence of complementary findings from both modalities.

Initial reports suggest a potential key benefits of PSMA including a lasck of influence of uptake in the post-biopsy setting compared to MRI. (18)
About lymph node involvement, several studies show that a large percentage of limph node metastases demonstrate very high levels of PSMA; literature also report the tendency of micrometastatic nodal disease to escape from detection.

Another source of possible limitations is the possibility of primary prostate tumor PSMA-negative. Nowadays, data to establish the receptor status of tumor cells in these patients, unfortunately are still few.

Historically, PSMA-based radiolabeled ligands were already investigated in 2005 at Johns Hopkins University (18) the first specific PSMA-targeting probe was 111In-capromab pendetide (Prostascint®), a 111In-labeled anti-PSMA antibody, its real diagnostic application was limited due to its binding to an intracellular domain of PSMA. This kind of biochemical feature explain the high non-specific nature of its uptake, because it is possible only after internalization or in cells with disrupted membranes. Since then, many and interesting PSMA-targeted PET tracers have been developed from different study groups, showing promising results for accurate staging of primary PCa and re-staging after biochemical recurrence, even in case of low PSA values.

Today the most used diagnostic PSMA ligand in Europe is 68Ga-PSMA-11 (also known as 68Ga-PSMA-HBED-CC).

Very promising results are demonstrated about theranostic variant of PSMA (PSMA-617), allows for diagnostic imaging using the 68Ga coupled tracer and for therapy using the beta-emitter lutetium-177.

In international literature, 177Lu-PSMA-617 is reported as an optimally tollerate and effective therapy, with a PSA decline in 75% of patients and a decline of 50% or greater in 50% of patients, with an increased overall survival, after two cycles of therapy. (19)

In parallel with diagnostic and therapeutic applications, PSMA ligands could also be used as a radio-guided surgery (RGS) option for PCa patients.

Radical prostatectomy still represents the gold standard technique for this kind of patients; sometimes, residual disease and/or micrometastases can not be accurately identified and removed during surgery time, leading to potential recurrence of the disease.
In this sense, as already proven by RGS efficacy in patients with breast cancer or cutaneous malignancies, PSMA-based tracers could provide real-time information to the surgeon, as it concern about resection margins and extent of the disease. (20)

11C-Acetate

Acetate is a metabolic substrate of β-oxidation and fatty acid precursor, successively converted to Acetyl-CoA.
In cancer cells, the principal metabolic role of Acetyl CoA is to partecipate at sterol and fatty acid synthesis, via fatty acid synthase enzime (FAS). (21)

PCa cells show an increased need for acetate, related to the increased need of lipid membranes; in this scenario a FAS over-expression is observed and it's correlated to PCa aggressiveness and Gleason score. (22)

At the beginning, acetate, has been radiolabeled with 11C for PET imaging to quantify myocardial oxidative metabolism, due to its radioactive side 11C-acetate present a biodistributive advantage in PCa imaging, according with its major elimination through respiratory system and not through urinary one.
At the same time, as for other radiopharmaceuticals, it shows a limited ability to differentiate between PCa and BPH; several studies also report that the evaluation of limph nodes metastasis provide overall a limited accuracy. (23) Due to these evidences, is reported a non optimal utilization of 11C-acetate PET in the initial phase of PCa diagnosis and staging.

On the other side, given the similar uptake mechanism of 11C-acetate PET and radiolabeled choline, some studies directly compared the two radiofarmaceuticals, finding stackable results. (24) 11C-acetate PET i salso described as a promising diagnostic option in the setting of bone metastases evaluation, thanks to good results after comparison with 99mTc-biphosphonate imaging in the detection of bone lesions. (25)

18F-Fluciclovine

Another class of interesting PET radiofarmaceuticals in PCa is radiolabeled amino acids (AAs).

Natural AAs are biological molecoles that play a central role in some cellular processes: including protein synthesis, energy metabolism, cell signaling, carbon sources for cell growth and neurotransmission.
Since 1990 radiolabeled AAs have been used for human imaging and there is a brillant interest

In this field, due to recent evidence of the role of AAs transporters and AAs in tumor metabolism. (26) in PCa there is evidence of an AAs transport and metabolism up-regulation, related to the higher need for protein synthesis and energy in cancer cells.
The most extensively investigated synthetic amino acid in PCa is anti-18F-FACBC (or 18F-Fluciclovine), recent and very promising studies underline the advantages of this kind of tracer also due to its relatively low levels of urinary excretion, simplifing imaging of the pelvis. (26)

Dinamic studies recommend an early imaging, because 18-Fluciclovine showed an early peak and reaches a plateau between 15 and 20 minutes. (27)

There is a solid evidence of accurate detection of PCa within the gland itself and in pelvic lymph node metastases, in suspected recurrent disease scenario associated to biochemical failure.
In this setting 18F-Fluciclovine showed a sensibility/specificity superiority compared to some others radiological and nuclear medicine investigations; such as CT, radiolabeled anti-PSMA antibody 111-In-capromab pendetide (Prostascint) and also 11C-choline. (28)

METASTATIC DISEASE

TRADITIONAL BONE SCAN vs 18F-NaF PET SCAN

Prostate Cancer (PCa) is the leading cause of bone metastases in men, this fact reveal the foundamental importance of bone involvement in the risk assestment evaluation of PCa patients. (29) Skeletal evaluation is also one of the prior factors in defining an optimal therapeutic management.

To better understand the difference between radiopharmaceutical options, is useful to define a general bone metastases pattern.

Generally there are two main types of bone reaction to a metastasis: bone reabsorption mediates by osteoclast and bone material affixing mediates by osteoblasts; the balance between these processes determinate the characteristics of a bone lesion and its radiological appearance.
In particular, osteolytic modifications are expression of an increased osteoclast activation, accompained by a concomitant decrease in the osteoblastic side: the final effect leads to an abnotmally high rate of bone reabsorption.
On contrary, osteoblastic lesions are related to an increased bone's formation around tumour cell

deposits, according with a major osseus apposition over the osteoclastic activity.
So we can define three kind of bone metastases: osteolytic, osteoblastic and mixed (containing both osteolytic and osteoblastic features). (30)
Previous studies show a prostate cancer's osteoblastic trend, related to cellular factors including an increased affinity for bone marrow endothelium, a PSA role in osteoblast proliferation and at the same time an osteoclast precursors apoptosis. (31)

First imaging technique option, in bone evaluation, is 99mTc-MDP planar scintigraphy with possibility of tomographic acquisition using SPECT (single photon emission computed tomography), or hybrid SPECT/CT, to increase diagnostic accuracy. (32)
Diphosphonates (DP) are synthetic organic compounds, similar with inorganic pyrophosphate at chemical structure level. The principal DP uptake mechanism in the skeleton is related to a chemo-adsorption on the surface of hydroxy-apatite crystals mediated by chemical bonds .
DP's accumulation in the bone is principally lead by blood flow and bone's avidity for the tracer: the focal uptake observed at bone scintigraphy reflect a massive formation of new bone respect to normal areas. This kind of evidence may explain the presence of a local damage (malignant or benign origin) stimulating osteoblastic way, or a physiological growth structure, as symmetrically noted in infant's metaphysis.
Image qualuty of bone scintigraphy is related to the ratio between absolute retention of the reacer in nbone and acrivitu in soft tissues.
Sensitivity is related to intensity of osteoblastic activation, so BS is not indicated in pure osteolytic bone involvement characterized by a low or absent psteoblastic reaction. (33)
This kind of low sensitivity is classically observed in patients affected by Multiple Myeloma; in case of large osteolytic areas BS imaging could show some "cold defined areas", representing the exact counterpart of pathological hot spots referable to high bone remodelling. (34)

Bone Scan (BS) is indicated in the first assestment of PCa patients in case of PSA levels >20 ng/ml (or PSA >10 ng/ml in T2), Gleason score ≥8, or in T3/T4.
Instead, since probability of bone involvement still low BS is not indicated, such as in low-risk PCa patients.
BS strenghts certainly are large availability, relatively low costs and a simple, well tollerated procedure; in addition it report high sensitivity in identifying bone metastases. (35)
Important downsides are: lack of specificity in bone metastasis vs benign bone conditions differentiation and poor spatial resolution. (36)

The second bone imaging option is 18F-NaF PET/CT, which benefits first of all from the known better spatial resolution of PET vs SPECT. (37)
18F-NaF has similar uptake mechanism to 99mTc-MDP, related to osteoblastic activity and blood flow, but several studies confirm better pharmacokinetic properties.
For example, a major advantage of NaF respect to 99mTc-diphosphonates is a higher first pass extraction and consequent faster bone's uptake. Some studies comparate NaF and MDP, demostrating the higher PET's diagnostic accuracy respect to traditional procedures: this improvement is determined by the detection of a large number of additional bone lesions, mostly identified in the spine. (38)
Comparing the characteristics of both techniques we can conclude for a superiority of 18F-NaF PET/CT vs 99mTc-MDP bone scan in the detection of osseus metastases;
but in clinical practice the tecnique is not yet widely implemented, probably because of some practical problems.
Some of these are the lower avilability of the radiopharmaceutical and of PET/CT scanners compared with γ-cameras, in addition to the higher costs. (39)

All these aspects, today, still place BS in a position of utility in diagnostic step of PCa bone metastasis.

LOOK TO THE FUTURE

NEW RADIOTRACERS

Molecular imaging using high-resolution SPECT PET has advanced elegantly and has steadily gained

importance in the clinical and research arenas. (40-42) As nuclear imaging technology continues to advance, the role of radiopharmaceuticals becomes ever more important. (43-45)

By its very nature, nuclear medicine always has an eye towards the future; it is a medical discipline that seeks new (biochemical) ways to better face the challenges it faces. (46)
In this perspective, we must look at the "flowering" of many new radiopharmaceuticals for diagnostic and therapeutic use. (47)

Radiolabeled Bombesin Analogues

Gastrin releasing-peptide (GRP) is a member of "bombesine-like peptides" family, it's a 27-amino acid peptide with a bombesin similar structure.

GRP explicate its role binding specific receptors (GRPRs), and precisely the interaction between GRP-GRPRs lead to a fitogeni activity now known to indce cell growth in various tumors. (48)

The recent great interest around these peptides is justified by the discovery that many primary cancers, including PCa, shows an overexpression of GRPRs.

In particular, GRPRs are overexpressed on the cell membranes of prostatic intraepithelial neoplasias (PIN) and in primary PCa; recalling the specificity issues of the previously mentioned radiopharmaceuticals recalling the specificity issues of the previously mentioned radiopharmaceuticals, of great impact seems to be the evidence that this kind of cellular behavior does not happen in normal prostate tissue and, in most cases, in benign prostate hyperplasia. (49)

Radiolabeled bombesin analogues targeting GRPRs could be a new valid example of teragnostics in nuclear medicine: through a diagnostic use of selective PCa imaging using β+ emitting isotopes for PET, and exploiting the possibilities of β- isotopes for a peptide receptor radionuclide therapy (PRRT).

This would open up new scenarios in the field of systemic prostate cancer therapy strategies. At the moment, 68Ga-RM2 (formerly also known as BAY86-7548) is considered the most promising radiolabeled bombesin analogue translated into the clinical phase. (50)
Interesting results have also been reported by other bombesin analogues for PCa patients: 18F-labeled BAY-864367 and 64Cu-CB-TE2A-AR06; in addition to 68Ga-NeoBOMB1 which shows the most promising results in preliminary studies. (50)

Obviously, this whole *carnet* of encouraging new radiopharmaceuticals needs extensive confirmatory studies.

Androgen Receptor Targeting Radiopharmaceuticals (FDHT)

PCa is an androgen-dependent malignant disease and the androgen receptor plays a pivotal role in many patological processes of this kind of malignancy.
The treatment strategy in the presence of hormone-sensitive advanced PCa is centered on testosterone's depletion; this type of result is obtained with surgery, whether or not associated with anti-androgen, or through the use of gonadotropin-relelasing hormone (GnRH) analogues that produce chemical castration as an ultimate goal.

After an initial response to androgen depletion and at the same time a reduction in PSA with the observation of a tumor regression, it is possible that a negative evolution occurs in the natural history of the disease. (38)
Approximately 1-3 years after initiation of therapy there may be a progression to castration-resistant prostate cancer (CRPC), characterized by the transition to the lethal phase of this disease. However, the androgen receptor aintains high expression in CRPC and assume a playng role, independently from the androgen deprivation. (51)

PET imaging of androgen receptor expression could represent a very interesting approach to guide the therapeutic management of these kind of patients.
The most used PET radiopharmaceutical targeting androgen receptor is 18F-fluoro-dihydrotestosterone (18F-FDHT). (52)

Despite some encouraging results, its role still needs to be fully explored.

HYBRID SYSTEMS: PET/MRI

Until a few years ago, morphological information of conventional radiology and functional information of nuclear medicine were seen as two mutually exclusive choices. The present and above all the future, on the other hand, go in another direction: that of complementarity. Technological development and data evidence show that the best possible perspective is that of hybrid systems.

From this point of view, we can certainly say that MRI and PET have many strengths and some weaknesses in prostate cancer evaluation.
mpMRI combines multimodal MRI sequences and guaranteed excellent anatomical visualization of the gland structure and adjacent organs, with high resolution and good soft-tissue definition. It add to classic MRI imaging some important informations about cellularity (using DWI), hypervascularity and neoangiogenesis (using DCE) and metabolites' evaluation (using MRS).

On the other hand, PET radiopharmaceuticals works for a better visualization of the gland about its biochemical and receptorial funcioning, analizyng the whole body with high sensitivity. MRI is considered a gold standard in primary cancer study, PET is most useful in the biochemical recurrence scenario and in detection of distant localizations of metastatic PCa.
Hybrid PET/MRI combines the complementary information related from each modality and offer some additional benefits in PCa patient: reduction of radiation exposure due to use of MRI instead CT, increased diagnostic accuracy deriving by the peculiar features of two brilliant techniques.

PET/MRI has cleary the potential of becoming the preferred imaging modality in PCa in the next decade, but wide prospective studies are programmed to clarify the benefits of the combined approach in the practical clinic. The hope is that this tool can change for the better the PCa diagnostic imaging management. (53)

NUCLEAR MEDICINE PROSTATE CANCER THERAPY

223Ra-dichloride

223Ra is a targeted alpha-therapy proposed in metastatic castration-resistant prostate cancer, with symptomatic bone metastases and without known visceral metastases.
It shows a survival benefit in this specific scenario.

In order to be candidates for this type of therapy, clinical cases must satisfy certain conditions. First of all, patients must present at least two sites of bone metastases demonstrated at bone scintigraphy with 99mTc-diphosphonate. As an alternative, due to an a higher diagnostic performance, 18F-NaF PET/CT can be used in alternative to classical bone scan.
To exclude visceral metastases, a computed tomography (CT) imaging and/or PET/CT after administration of 18F/11C-choline or 68Ga-prostate-specific membrane antigen (PSMA) must be performed.
These imaging techniques are also able to verify the presence of nodal disease (the presence of malignant lymph nodes greater than 3 cm short axis represents exclusion criteria for treatment). All these diagnostic studies have to be done within 3 months before starting therapy.

Before using 223Ra-dichloride it is necessary to ascertain the presence of an adequate medullary function; this is done through an in-depth haematological assessment at baseline and prior to every radiopharmaceutical administration.

The evaluation of the response after a therapy with 223Ra-dichloride consists in bringing together the information deriving from different disease markers.

Among those of biochemical type, the most important is certainly the ALP serum: it represents an osteoblastic activity biomarker and is considered the most accurate for evaluating the response to treatment.

Much more than serum PSA, which concerns little specifically the therapeutic field of the bone

scenario and finds its usefulness in the biochemical monitoring of PCa in general.

Another important answer is provided by the bone scan which is useful for at least two reasons: the evaluation of the patient at the "end of the treatment" but also "ad interim", in the event that there are strong suspicions of a bone disease progression.

Last but not least, the evaluation of pain is strictly correlated, in the case of its improvement in correlation with therapy, to the patient's quality of life.

177Lu-PSMA

Within the whole management of PCa, castration-resistant metastatic prostate cancer (mCRPC) represents one of the greatest challenges from a therapeutic point of view; this is because by definition it refers to that part of patients resistant to the androgen-deprivation strategy.

In these cases there is a progression of the pathology and a relatively limited possibility of further therapeutic choices.

To date, it is possible to select patients for docetaxel, sipuleucel-T, abiraterone, and radium-223 therapies; but unanimously it is open to novelties that guarantee better management of this stage of disease.

As previously reported, PSMA appears to be a membran glycoprotein that exhibits a distinct overexpression in prostate cancer cells. Due to its high specificity for prostate cancer, PSMA is a promising target for molecular imaging and therapeutics.

Radionuclide therapy has been studying the possibilities of using PSMA for several years, specifically the most promising radiopharmaceutical to date seems to be the PSMA-617 ligand conjugated with lutetium-177 (177Lu-PSMA-617). It is comprised of PSMA-617, a small molecule designed to bind with high affinity to PSMA and that target prostate cancer cells, the Glu-urea-Lys PSMA binding motif, and the DOTA/DOTAGA chelator linked with lutetium-177. It releases energetic beta-particles that destroy cancer cells at the disease site. (54)

On the basis of the data available to us, in terms of pre- and post-therapy monitoring and from the side effects point of view, we can deduce that only a minority of patients had high-grade hematological toxicities, and that were dose-dependent. Typically, platelets nadir around four weeks after therapy, while the leukocyte count nadirs around two weeks after therapy.
Cytopenias are generally transient, with counts eventually returning to normal ranges. Less serious, but more common, side effects included nausea, fatigue and xerostomia. (55)

Sun M. et al. conducted a study of the international reference literature using as inclusion criteria:

clinical trials involving more than 10 patients and solely utilizing 177Lu-PSMA-617. Seventeen studies were included in the final analysis. Variables documented included the number of patients, the total therapeutic dose administered, the percentage of any prostate-specific antigen (PSA) decline, the percentage with PSA decline exceeding 50% baseline, and toxicities.

Overall, a majority of patients responded to therapy, and in the prospective studies, survival was found to be upwards of one year. (56)

Based on these data and waiting for more and more confirmations, 177Lu-PSMA-617 is emerging as a viable and effective therapy in patients with progressiven metastatic prostate cancer, with a majority of patients responding to the therapy. (57)

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