San Doctor

SUMMER 2020

^{177}Lutetium prostate specific membrane antigen (PSMA) radioligand therapy in patients with advanced prostate cancer

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Dr Edwin Szeto is an experienced Nuclear Medicine Physician with a particular interest in radionuclide therapy. Having spent many years at St Vincent's Hospital where he led radionuclide therapy (including introducing radioimmunotherapy in relapsed NHL), Dr Szeto now leads the new Theranostics Services at San Radiology & Nuclear Medicine. Dr Szeto consults at Suite 306 San Clinic.

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INTRODUCTION

Patients with metastatic castration-resistant prostate cancer (mCRPC) who subsequently fail currently available options of hormonal agents and chemotherapy, have a grim prognosis. ^{177}Lutetium-PSMA (Lu-PSMA) is a promising new treatment for these patients.

HOW DOES IT WORK?

PSMA is a type II transmembrane glycoprotein that is expressed in the cytosol of normal prostatic tissue and highly overexpressed on the membrane in prostate cancer cells. The extent of PSMA expression is positively correlated with tumour grade and disease stage, thus rendering it an ideal target for imaging. Furthermore, its low presence in the bloodstream and its internalisation and retention within tumour cells make it an ideal target for treatment. In the era of personalised medicine, combining imaging diagnosis with targeted radionuclide therapy (Theranostics) is very attractive.[1,2]

For imaging, PSMA (radiolabelled with either ^{68}Gallium or ^{18}Fluorine) PET scanning has already become clinically accepted as the most sensitive imaging modality available for detecting prostate cancers (see Figure 1[3]).

For treatment, PSMA is radiolabelled with ^{177}Lutetium which is an ideal radionuclide for therapy, as it has high energy beta rays with short tissue penetration depth for effecting targeted radiotherapy, as well as emitting low energy gamma rays which are used for post-treatment imaging to verify sites receiving treatment and for dosimetry calculations.[4]

SAFETY AND EFFICACY OF LU-PSMA

Since 2014 there have been multiple retrospective studies demonstrating the low toxicity and efficacy of Lu-PSMA with significant declines in PSA. The largest study involved 145 patients with mCRPC in 12 therapy centres in Germany. There were no therapy related deaths. The overall biochemical response, defined as > 50% PSA reduction, was reported in 45% of patients. Grade 3-4 haematologic toxicity was reported in 12%.[5]

A meta-analysis comparing the efficacy of Lu-PSMA therapy and third-line treatment for mCRPC patients was published in 2018.[6] In twelve studies including 669 patients receiving Lu-PSMA, 43% had a best PSA decline of >50% following treatment. In sixteen studies including 1338 patients receiving third-line treatment, 21% had a best PSA decline of >50%. Lu-PSMA gave objective remission more often than third-line treatment (31 of 109 patients vs 43 of 275 patients, p=0.004, X2 test). Median survival was longer after Lu-PSMA than after third-line treatment, but the difference was not significant (mean 14 vs 12 months, p=0.32, t-test). Adverse effects caused discontinuation of treatment more often for third-line treatment than for Lu-PSMA (22 of 66 patients vs 0 of 469 patients, p<0.001, X2 test).

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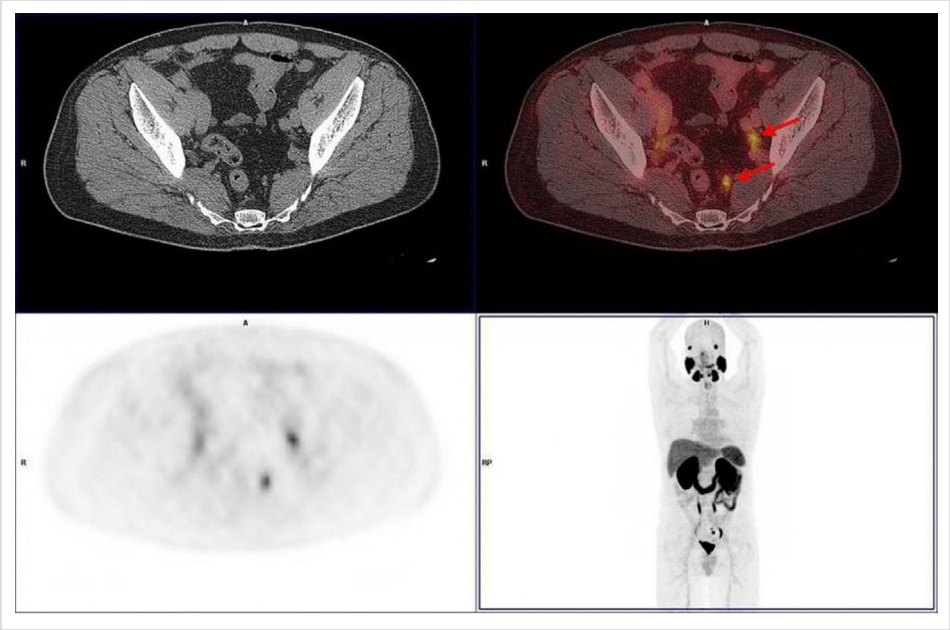

Figure 1: CT scans did not reveal any morphological abnormalities of pelvic lymph nodes which were, due to their high PSMA avidity, identified as suspicious only after the PET scan.
- Wehrmedizinische Monatsschrift 2018; 62(8): 266-270

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The results of the first phase 2 prospective study of Lu-PSMA therapy (Peter MacCallum Cancer Centre) were published in 2018.[7,8] In this study (initially performed in 30 but expanded to 50 patients) with progressive disease following standard treatment including taxane-based chemotherapy and novel androgen receptor pathway inhibitors (ARPI), PSA decline of at least 50% was achieved in 64% (32 of 50 patients) with attributable Grade 3-4 anaemia (10%), thrombocytopenia (10%) and neutropenia (6%). Improvements in pain severity and interference scores were recorded at all time points. Median overall survival was 13.3 months (95%CI 10.5-18.7), with significantly longer survival of 18.4 months (95%CI 13.8-23.8) in patients achieving a PSA decline >50%. At progression after prior response, further Lu-PSMA was administered to 15 patients (30%) with PSA decline of > 50% in 11 patients (73%), compared to 4 of 21 patients (19%) receiving other systemic therapies on progression.

There is currently no completed randomised data on the efficacy of Lu-PSMA in mCRPC. There are two ongoing multicentre randomised trials.

One is an international, prospective, open-label, multicentre randomised phase 3 trial (VISION trial, NCT03511664) where 750 patients with mCRPC who previously received at least one novel ARPI and 1-2 taxane-based chemotherapy drugs are randomized 2:1 to receive Lu-PSMA or physician-determined best supportive care (including novel ARPIs).

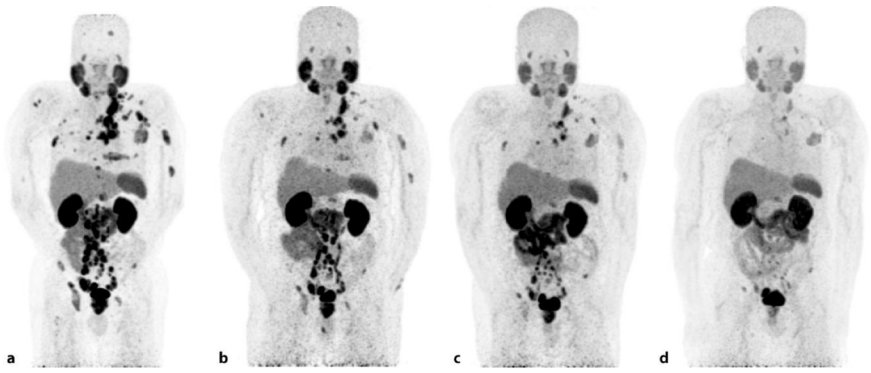

Figure2: ^{68}Ga-PSMA PET scans of a patient with mCRPC. (a) Baseline, PSA 100µg/L; (b) After 2 cycles of ^{177}Lu-PSMA, PSA 190µg/L; (c) After 4 cycles of ^{177}Lu-PSMA, PSA 52µg/L; (d) After 6 cycles of ^{177}Lu-PSMA, PSA 19µg/L. - Tijdschr Urol 2020; 10: 141-146.

The other is an Australian randomised phase 2 trial comparing Lu-PSMA with second-line chemotherapy (cabazitaxel) in 200 patients with mCRPC following progression on docetaxel +/– novel ARPIs (TheraP trial, NCT03392428). Both trials are scheduled to be completed in 2021. However, the Australian trial recently reported initial results that the PSA response rate was higher in those assigned to Lu-PSMA than cabazitaxel (65/99 [66%; 95%CI 56-75] vs 37/101 [37%; 95%CI 27-46]; p<0.001) with relatively fewer Grade 3-4 adverse events and PSA-progression free survival favouring Lu-PSMA.[9]

SUMMARY

Lu-PSMA is safe with low toxicity and has much promise to become a standard treatment in patients with mCRPC, and although current clinical and research applications are restricted to patients who have progressed after conventional treatments, I envisage future trials with Lu-PSMA used in the pre-chemotherapy setting.

Lu-PSMA is currently authorised for compassionate use via the TGA Special Access Scheme and is available at Sydney Adventist Hospital from early 2021.

References available on request.

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to visualise the shoulder pathology and to instrument for debridement and/or repair.

Rotator cuff repair begins with inspection followed by preparation of bone surfaces and mobilisation of tendon.

Suture anchors are placed in the original insertion site of the tendon and tendons are sutured in place.

Patients are placed in a sling and often stay one night in hospital.

REHABILITATION

This is dependent on surgeon preference and also on a number of factors including; size/degree of tear, age of patient, quality of tendon, quality of bone, quality of repair.

Generally rehabilitation is divided into three phases:

- **Phase 1** (0-6 weeks) Mostly in a sling. No driving. Gentle passive exercises
- **Phase 2** (6-12 weeks) Exercises to improve active range of motion
- **Phase 3** (>12 weeks) Strengthening exercises.

Patients should be advised that they will continue to show improvement up to 12-18months post-surgery.

RISKS

These include re-tear (~10-20%), stiffness, infection (<1-2%), bleeding (<1%), nerve injury (<0.5%).

PROGNOSIS

Satisfaction post rotator cuff repair is around 90-95% in most series.

Factors that reduce the rates of success include:

- Larger tears
- Workers compensation status
- Patient age >65
- Smoking.

OTHER PROCEDURES

Tendon Transfer

Tendon transfers involving the latissimus dorsi or pectoralis major are sometimes indicated in younger active patients with irreparable rotator cuff tears.

Reverse Shoulder Arthroplasty

Patients with evidence of arthritis secondary to long standing rotator cuff disease are candidates for reverse shoulder replacement. This procedure reliably provides pain relief in longstanding arthritis.

FUTURE DEVELOPMENTS

Recent developments have focused on slowing down and/or arresting degenerative changes in tendon as well as promoting healing.

Tissue grafts are being used to augment repair of tendon or replace tendon defects. Patches containing biological substrate components including collagen can be inserted during surgery.

Injections of growth promoting substances such as Platelet Rich Plasma or growth factors are being trialed to promote healing.

References available on request.

COVID -19 update

Adventist HealthCare remains vigilant to the changing community circumstances with the Hospital clinical and management teams taking advice from NSW Health, the Australian Government and the Commonwealth Department of Health.

Latest access, mask wearing and visitor arrangement currently in place at the San are detailed at wwww.sah.org.au/coronavirus-information.