Oncology

An exceptional response to $^{177}$LuPSMA undermined by neuroendocrine transformation

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**ABSTRACT**

Approximately 25% of patients who have undergone extensive systemic therapy for advanced metastatic castration-resistant prostate cancer (mCRPC) develop treatment-associated neuroendocrine prostate cancer (NEPC). $^{177}$Lu-prostate specific membrane antigen (PSMA) is an emerging alternative therapy for mCRPC patients who have exhausted other systemic therapy options; however, cells with neuroendocrine differentiation do not express PSMA and are not affected by this treatment. This case highlights an exceptional response of skeletal metastases to $^{177}$LuPSMA that is undermined by neuroendocrine transformation in the liver.

**Introduction**

Approximately 25% of patients who have undergone extensive hormone therapy and/or chemotherapy for advanced metastatic castration-resistant prostate cancer (mCRPC) develop treatment-associated neuroendocrine prostate cancer (NEPC). We present a case of a patient who has undergone extensive treatment including an emerging therapy, $^{177}$Lu-prostate specific membrane antigen (PSMA), who develops rapidly progressive incurable disease.

**Case presentation**

A 73-year-old male patient developed nausea and lethargy following his second cycle of Lutetium $^{177}$PSMA for metastatic castration-resistant prostate cancer (mCRPC). Seven years prior he had undergone robotic prostatectomy for Gleason $5 + 4 = 9$ adenocarcinoma with extraprostatic extension. He received intermittent doses of androgen deprivation therapy (ADT) over the following years. Twelve months prior to this presentation, he was referred for consideration of docetaxel chemotherapy for metastatic hormone-sensitive prostate cancer. The patient declined this treatment option and continued with ADT. Three months thereafter his cancer became castration-resistant. He received four cycles of docetaxel chemotherapy followed by five cycles of cabazitaxel chemotherapy with no appreciable response.

The patient’s PSA peaked at 150 μg/L (reference range: 0.3–6.5 μg/L). He received two cycles of $^{177}$LuPSMA therapy, six weeks apart. Fig. 1 reveals the extent of the bone disease prior to the commencement of $^{177}$LuPSMA therapy. Fig. 2 reveals extent of the bone disease after the $^{177}$LuPSMA therapy.

Following the second cycle of radiologically and biochemically successful treatment, the patient complained of xerostomia, nausea and lethargy, all common side effects of $^{177}$LuPSMA. His PSA had decreased to 0.5 μg/L (<1% of the baseline). However, the companion diagnostic PSMA scan of his liver, performed with the second $^{177}$LuPSMA revealed multifocal hypodense changes without PSMA activity. Within a fortnight, his liver function tests started to deteriorate. A liver ultrasound confirmed marked heterogeneity with nodularity. An attempted ultrasound-guided liver biopsy was aborted owing to brisk bleeding with the placement of the coaxial needle prior to the biopsy. His serum chromogranin A level was 214 μg/L (reference range <102). Fig. 3 reveals the MRI used to confirm diffuse metastatic liver disease.

Based on the rapid development of widely disseminated, small homogenous metastases throughout the liver and in no other visceral organs, in the context of a very low PSA and high Chromogranin A (with Chromogranin A being a well-documented bio marker for neuroendocrine tumour), the diagnosis of neuroendocrine transformation from prostate adenocarcinoma was discussed with the patient. He proceeded...
to treatment with carboplatin and etoposide chemotherapy. Sadly, his cancer did not respond and he died within weeks from liver failure due to the burden of metastatic disease.

Discussion

Prostate cancer is the most common cancer diagnosed in men in developed countries. Few prostate cancers harbour neuroendocrine variants at diagnosis. The vast majority of prostate cancers are prostatic adenocarcinoma which behave as a chronic disease and can be treated with standard therapies. Treatment of metastatic prostate cancer has become progressively complex and incorporates the use of androgen deprivation therapy, systemic taxane chemotherapy, and targeted androgen therapy. These treatments can be used in varying combinations over a number of years to slow the progression of metastatic prostate cancer whilst preserving the patients’ quality of life.

Approximately 25% of patients who have undergone extensive hormone therapy and/or chemotherapy for advanced metastatic castration-resistant prostate cancer (mCRPC) develop treatment-associated neuroendocrine prostate cancer (NEPC). Common features of treatment-associated NEPC include disproportionately low PSA levels in combination with rapid disease progression and high burdens of lytic bone and visceral metastases. Serum levels of the neuroendocrine markers, chromogranin A, neurom-specific enolase and gastrin-releasing peptide, are usually elevated. Chromogranin A is considered to be both specific and sensitive and is the most commonly used biomarker in neuroendocrine tumour differentiation. The only factor associated with more rapid disease transformation from prostatic adenocarcinoma is an initial Gleason score $\geq 8$.\(^1\,^4\)

Tissue diagnosis via metastatic biopsy can reveal different pathological subtypes of neuroendocrine tumours which portend various rates of survival, but all are invariably fatal. Treatment is currently based on systemic platinum-based therapy which offers a rapid but unsustainable response.\(^1\) This empiric treatment is based on its use in other small-cell tumours, particularly those arising from the lung, and is not as successful in treating NEPC. To date there is a lack of published clinical trial data for the successful treatment of NEPC. Some trials are currently focusing on genomic sequencing of NEPC to differentiate treatable and targetable variants.\(^17\)

$^{177}$Lu-prostate specific membrane antigen (-PSMA) therapy is an emerging treatment for patients with mCRPC cancer after exhaustion of other systemic therapies. $^{177}$LuPSMA is a radiolabelled isotope which binds with high affinity to the PSMA, a transmembrane glycoprotein which is expressed in prostate epithelium and over-expressed, more than one hundred-fold, in prostate cancer cells. This enables targeted delivery of beta-radiation to malignant cells. Many trials of this treatment modality have included heavily pre-treated patients who have already received multiple chemotherapy and hormonal agents. Responses to $^{177}$LuPSMA treatment include a reduction of PSA of $\geq 50\%$, an improved quality of life, and decreased levels of pain.\(^4\) Adverse effects of $^{177}$LuPSMA are few and can be anticipated due the distribution of PSMA expressing cells such as in salivary glands resulting in xerostomia, and in the small intestine resulting nausea and gastrointestinal upset. Since renal tubules also express PSMA, this therapy is safe for administration to patients with mildly decreased renal function (eGFR $\geq$ 40mL/min) without obstruction. Patients with sufficient haematological reserve, with platelets $\geq 75 \times 10^9$/L and neutrophils $\geq 1.5 \times 10^9$/L, can also safely receive this treatment. Transient increase in pain at the sites of metastases and fatigue can be expected.\(^3\,^5\)

Cells with neuroendocrine differentiation do not express PSMA and...
are not affected by $^{177}$LuPSMA. Based on case studies which have shown patients to have treatment-associated neuroendocrine prostate cancer some clinicians recommend FDG PET/CT imaging to further select patients for PSMA targeted therapy.

**Conclusion**

This case has demonstrated an exceptional response to $^{177}$LuPSMA for previously identified bone metastases with near complete resolution of these on PSMA PET/CT scan and a drop to <1% baseline of the PSA. However, this response has been undermined by the transformation of the metastases in the liver to neuroendocrine tumours that do not respond to $^{177}$LuPSMA.

**Consent**

The patient’s wife provided proxy consent for anonymised clinical information and imaging to be included in this paper. The written consent is stored in the patient’s hospital record.

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**Declaration of competing interest**

None.

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