

# Peptide receptor chemoradionuclide therapy in small cell carcinoma: from bench to bedside

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Received: 12 March 2014 / Accepted: 31 July 2014 / Published online: 16 August 2014  
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## Abstract

**Purpose** Small cell cancers (SmCC), whether pulmonary (SCLC) or extrapulmonary, have a poor prognosis unless localised at diagnosis. Given a proportion of these cancers express somatostatin receptor subtype 2 (SSTR2), we aimed to investigate the efficacy of targeted peptide receptor chemoradionuclide therapy (PRCRT).

**Methods** In this preclinical study, we used a SCLC xenograft mouse model with high expression of SSTR2 to investigate the effect of peptide receptor radionuclide therapy (PRRT) with chemotherapy compared to either alone. We subsequently explored the clinical utility in a patient with SmCC with high SSTR expression treated with PRCRT.

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Jeremy Lewin and Carleen Cullinane contributed equally to the results presented in this report.

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**Electronic supplementary material** The online version of this article (doi:10.1007/s00259-014-2888-2) contains supplementary material, which is available to authorized users.

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**Results** Robust expression of SSTR2 in NCI-H69 SCLC xenografts was documented by <sup>68</sup>Ga-DOTA-octreotate (GaTate) (tumour to background uptake ratio=35). The combination of PRRT using <sup>177</sup>Lu-DOTA-octreotate (LuTate) with carboplatin/etoposide (C/E) chemotherapy was more effective than either LuTate or C/E alone for regression of the NCI-H69 model (*p* value<0.05). PRCRT was associated with significantly prolonged survival versus PRRT (*p* value=0.0001) or chemotherapy alone (*p* value=0.0058). In the subsequent case study, a patient with relapsed SmCC with high SSTR2 expression on GaTate PET underwent PRCRT with radiosensitising etoposide with evidence of a complete metabolic response for 4 months.

**Conclusion** Given the limited treatment options in this setting, PRCRT is a promising therapeutic option for SSTR2-expressing SmCC.

**Keywords** SSTR2 · Xenograft · Peptide receptor radionuclide therapy · Small cell lung cancer

## Introduction

Small cell cancers (SmCC) are uncommon malignancies that arise from pluripotent stem cells that have neuroendocrine features. Although they more commonly arise from the lung (SCLC), given their cell of origin they can also arise from extrapulmonary sites (ESCC). Despite having a good response to front-line chemotherapy, usually with a platinum doublet, SmCC carries a dismal prognosis at relapse [1, 2]. Although salvage therapy is an option for those with good performance status, second-line chemotherapy is less effective. Topotecan, the best studied chemotherapy for relapsed SCLC, has shown a response rate between 7 and 24 % [1, 3], and a recent review of 21 studies (1,692 patients) showed an overall response rate of 17.9 % with a median survival of 6.7 months [4]. This is

supported by similar data in ESCC, which is generally thought to carry an even worse prognosis than SCLC [5]. Given the overall poor outcomes in patients with SmCC, experimental approaches including targeted therapies, cancer vaccines and novel cytotoxic agents have been researched with limited success.

The demonstration of somatostatin receptor subtype 2 (SSTR2) expression in SmCC cells [6–10] has led to interest in using targeted radiotherapy with radiolabelled somatostatin analogues [11]. This interest has been stimulated by the success of peptide receptor radionuclide therapy (PRRT) in the management of metastatic neuroendocrine tumours with high SSTR expression where high response rates and prolonged survival have been seen [12, 13]. The most frequently used radionuclide is  $^{177}\text{Lu}$ , but  $^{90}\text{Y}$  and  $^{111}\text{In}$  are alternatives. Each of these radionuclides can be chelated to octreotate by 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA).

Unfortunately, preliminary reports of PRRT outcomes in SCLC have been disappointing [11, 14, 15]. Our group has previously moved from using PRRT alone to the combination of PRRT with radiosensitising chemotherapy, which we have termed peptide receptor chemoradionuclide therapy (PRCRT). We initially reported this with high-administered activity  $^{111}\text{In}$ -diethylenetriaminepentaacetic acid (DTPA)-octreotide [16] but have since applied this approach to  $^{177}\text{Lu}$ -DOTA-octreotate (LuTate) PRRT [17]. Given the chemosensitivity of SmCC and the radiosensitising potential of carboplatin and etoposide, we postulated that PRCRT using these agents might be an effective treatment regimen. To test this hypothesis, we have used an SSTR2-expressing preclinical model of SmCC to evaluate the efficacy of PRCRT. The therapeutic potential of PRCRT observed in the preclinical setting was supported by a clinical case study in which PRCRT was investigated.

## Materials and methods

### Cell lines

The human SCLC line NCI-H69 cell line was obtained from American Type Culture Collection (ATCC) and the LX22 cell line was derived from SCLC tissue from a chemo-naïve patient as described previously [18].

### Radiopharmaceuticals

LuTate was prepared as described previously [19].  $^{68}\text{Ga}$ -DOTA-octreotate (GaTate) was synthesised as described previously [20, 21]. For  $^{90}\text{Y}$ -DOTA-octreotate (YTate),  $^{90}\text{Y}$  was purchased from PerkinElmer Inc. (Waltham, MA, USA) and [DOTA<sup>0</sup>, Tyr<sup>3</sup>]octreotate from ABX (Dresden, Germany) and

YTate then synthesised as for LuTate except using  $^{90}\text{Y}$  instead of  $^{177}\text{Lu}$ .

### Animal models

All animal experiments were performed with Institutional Animal Ethics Committee approval. Balb/c nude mice (Animal Resources Centre, Canning Vale, WA, Australia) were implanted subcutaneously with either  $5 \times 10^6$  NCI-H69 or LX22 cells in 50 % Matrigel. For the NCI-H69 efficacy experiment, once tumours reached a mean volume of  $330 \text{ mm}^3$  the mice were randomised into treatment groups of eight mice. Mice were treated intravenously with 30 MBq LuTate alone or in combination with 60 mg/kg carboplatin (Hospira Inc., Melbourne, VIC, Australia) and 12 mg/kg etoposide (Bristol-Myers Squibb, Mulgrave, VIC, Australia). LuTate was specifically chosen in the preclinical model given its short particle range (approximately 1 mm), which is appropriate to the small volume of xenografts in mice. The significantly longer path length of  $^{90}\text{Y}$  (approximately 1 cm) would provide suboptimal microdosimetry for such small tumours and significant whole-body irradiation of the mouse. A second cycle of therapy was given 3 weeks later.

### Positron emission tomography (PET) imaging

Tumour-bearing mice were injected intravenously with 14.8 MBq GaTate and 60 min later were anaesthetised using 2 % isoflurane in 50 % oxygen in air. The animals were then placed on the bed of a small animal PET scanner (Philips Mosaic) before being imaged over 10 min.  $^{18}\text{F}$ -Fluorothymidine (FLT) and  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) PET imaging were performed as described previously to assess cell proliferation and glycolytic metabolism, respectively [22]. Image reconstruction and quantitation were as previously described [22].

### SSTR2 immunohistochemistry

H69 tumours ( $220 \text{ mm}^3$ ) harvested from mice at 24 h following a single 20-MBq dose of LuTate were fixed in formalin and embedded into paraffin blocks. Tumour sections ( $4 \mu\text{m}$ ) were dewaxed before antigen retrieval was performed using 10 mM sodium citrate pH 6.8 in a pressure cooker. After quenching endogenous peroxidase activity with hydrogen peroxide, the slides were incubated with SSTR2 primary antibody (1:250; Abcam, ab134152), washed in phosphate-buffered saline (PBS) and then incubated with rabbit Envision+HRP (Dako, Campbellfield, VIC, Australia). Positively stained cells were visualised using the DAB chromogen.

## Data analysis

Percentage tumour growth inhibition (TGI) was calculated as  $100 \times (1 - \Delta T / \Delta C)$  where  $\Delta C$  and  $\Delta T$  were determined by subtracting the mean tumour volume in the vehicle and treated groups, respectively, on day 1 of treatment from the mean tumour volume on the day of the assessment. Statistical analyses were performed using GraphPad Prism Version 6.0 (GraphPad, La Jolla, CA, USA) with analysis of variance (ANOVA) followed by Dunnett's post hoc test to compare the tumour growth in the treated groups to the vehicle control. Differences in survival were determined using the Mantel-Cox log-rank test.

## Case study

The case study describes a patient with relapsed ESCC. The patient's tissue was analysed for likely tissue of origin using the gene expression profiling assay CUPGUIDE™ (Healthscope, Melbourne, VIC, Australia) and treatment with PRCRT was performed after receiving written consent.

## Results

### Preclinical tumour model characterisation

Initial studies aimed to characterise SCLC cell lines for their suitability for preclinical investigation of the efficacy of combining standard SCLC chemotherapy with PRRT using LuTate. As the LX22 model has previously been shown to exhibit sensitivity to the carboplatin/etoposide regimen [23], we investigated tumour expression of SSTR2 in this model using immunohistochemical staining and PET imaging with GaTate. A representative image of the immunohistochemical analysis is shown in Fig. 1a. Regions of the LX22 tumour stained positive at the cell membrane for SSTR2, consistent with heterogeneous expression of the cell surface receptor. Furthermore, the SSTR2-specific tracer was shown by GaTate PET imaging to be specifically taken up into LX22 tumours (Fig. 1b). Semiquantitative analysis of tracer uptake revealed a tumour to background (where the background was defined as a non-tumour region representing the blood pool) uptake ratio (TBR) of  $12.6 \pm 1.7$ .

The NCI-H69 SCLC cell line was also chosen for evaluation since it has previously been reported to express high levels of SSTR2 [24]. We therefore characterised SSTR2 expression as per the LX22 model. As seen in Fig. 1a (right panel), NCI-H69 tumours demonstrate very strong membrane staining for SSTR2 and this was consistent with the very high GaTate uptake in vivo shown in Fig. 1b. The TBR in this model was over 2.7-fold higher than in the LX22 model at 35

$\pm 9$ . In comparison, the TBR for the standard PET tracers FDG and FLT in this model were  $2.9 \pm 0.4$  and  $2.2 \pm 0.2$ , respectively. On the basis of its robust growth and high SSTR2 expression, the H69 model was used for the anti-tumour efficacy study.

### Preclinical combination studies

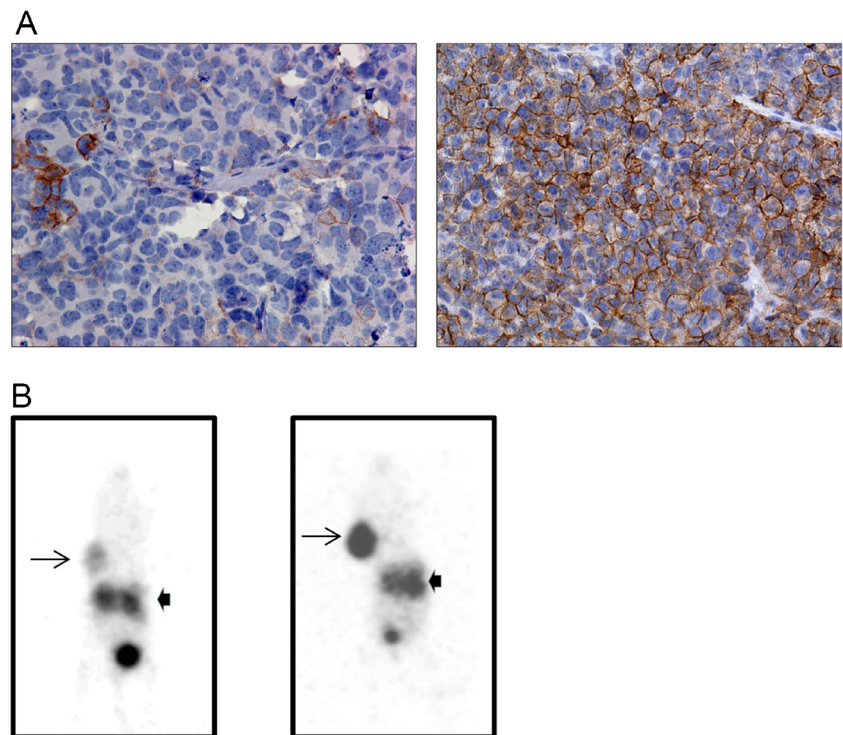
The most common chemotherapy regimen used in the clinic for SmCC involves the combination of a platinum agent with etoposide [25]. We therefore investigated the efficacy of combining PRRT using LuTate with this regimen in the NCI-H69 tumour model. Tumour-bearing mice received two cycles of therapy 3 weeks apart, consisting of 60 mg/kg carboplatin and 12 mg/kg etoposide [23] alone or in combination with 30 MBq LuTate. The chemotherapy treatment resulted in a maximum of 12 % body weight loss with two animals euthanised upon reaching 20 % weight loss on day 38 (Fig. S1). The addition of 30 MBq LuTate to chemotherapy did not have any additional impact on tolerability with only one animal exceeding 20 % weight loss on day 28. The effects of the therapy on tumour growth are summarised in Fig. 2. In this model, both the chemotherapy and LuTate treatments alone initially induced rapid tumour regression which was followed by a robust rebound in growth between days 10 and 20. Analysis on day 18 revealed tumour growth in all treatment groups was significantly inhibited compared to the vehicle control (Table 1). A second cycle of treatment on day 21 also resulted in tumour regression in the single therapy groups, albeit much less pronounced than following the first treatment cycle.

The combination of the two therapies caused significantly greater tumour regression than either treatment alone on day 18 (PRCRT versus PRRT or chemotherapy alone,  $p$  value < 0.05, Table 1) with no rebound of tumour growth observed between the two treatment cycles. The combination treatment also significantly prolonged survival as defined as the time until tumours reached a volume of 1,200 mm<sup>3</sup> compared to either treatment alone (Table 1).

### Translation into clinical utility

We also investigated the potential therapeutic utility of this strategy in a patient with relapsed SmCC. A 63-year-old woman with extensive stage SmCC was initially treated with carboplatin (AUC5) and etoposide (120 mg/m<sup>2</sup>) with a near complete response. After an 11-month period of surveillance, disease progression occurred. The patient was salvaged with six cycles of second-line chemotherapy (cyclophosphamide, doxorubicin and vincristine) and despite having a partial response the disease progressed within 2 months of finishing chemotherapy. Disease progression was complicated by rapidly deteriorating performance status secondary to bilateral

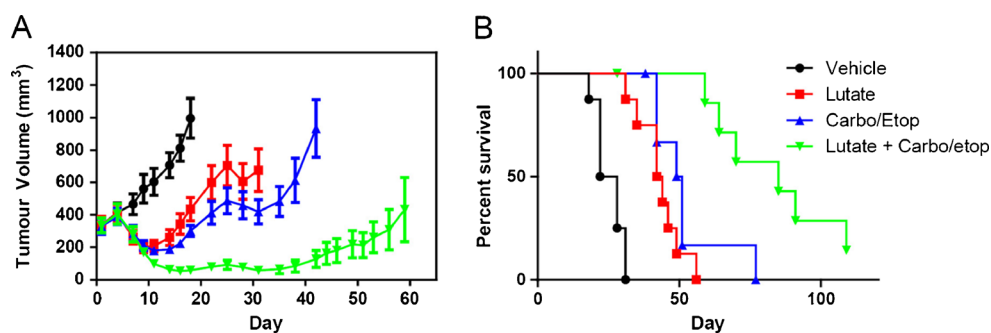
**Fig. 1** Characterisation of preclinical models for SSTR2 expression. **a** Representative images of LX22 (*left*) and NCI-H69 (*right*) tumour sections stained for SSTR2 expression by immunohistochemistry. Images are shown at  $\times 20$  magnification. **b** Maximum intensity projection PET images of LX22 (*left*) and NCI-H69 (*right*) tumour-bearing mice imaged 60 min post-injection with GaTate. The *thin arrow* indicates the position of the tumour and *arrowhead* the kidneys



lower leg oedema and acute kidney injury, with the patient's serum creatinine rising to 289  $\mu\text{mol/l}$ , related to bilateral hydronephrosis requiring insertion of bilateral ureteric stents.

Testing of the patient's biopsy using a gene tissue of origin assay (CUPGUIDE™, Healthscope) suggested a primary neuroendocrine tissue of origin. On that basis, a GaTate PET scan was undertaken and showed a primary cervical ESCC with extensive nodal metastatic disease and a moderate level of SSTR expression (equal or greater than hepatic parenchymal uptake, Krenning score 2–3) (Fig. 3, left panel; baseline fused GaTate PET/CT). An FDG PET showed spatially concordant disease of moderate avidity (Fig. 4, left panel; baseline fused FDG PET/CT). Based on limited therapeutic options, the

patient was offered experimental therapy under the compassionate use provision of the Australian Special Access Scheme. With her written consent, we elected to treat with YTate therapy based on the heterogeneous SSTR expression on GaTate PET/CT, reasoning that the more beta particulate emissions of  $^{90}\text{Y}$  (having a path length of up to 12 mm) would provide better crossfire effect than LuTate. Although potentially nephrotoxic, we reasoned that the patient's extremely poor glomerular function would minimise delivery of radiopeptide to the proximal convoluted tubules, which is the major site of renal uptake and thereby reduce the likelihood of significant renal irradiation with the first cycle of treatment. Accordingly, the patient was administered



**Fig. 2** Efficacy of LuTate combined with etoposide/carboplatin in the NCI-H69 SCLC xenograft model. NCI-H69 tumour-bearing mice were randomised to receive 30 MBq LuTate i.v. on days 1 and 21 (*square*), 60 mg/kg carboplatin i.v. on days 1 and 21 and 12 mg/kg etoposide i.v. on days 1–3 and days 21–23 (*up triangle*), vehicle (*circle*) or combination therapy of LuTate, carboplatin and etoposide as per single agent dose and

schedule (*down triangle*). Tumour volumes were determined 2–3 times weekly and the results are expressed in **a** as the mean  $\pm$  SEM ( $n=8$  animals per group). Graphs are shown for each group until the first animal reached a tumour volume ethical end point. Kaplan-Meier analysis of data is shown in **b**. The end point for the survival analysis was a tumour volume of 1,200  $\text{mm}^3$

**Table 1** Tumour growth inhibition

Treatment	Per cent TGI <sup>a</sup>	$p < 0.05^b$	Median survival (days)	$p$ value <sup>c</sup>
Vehicle			25	
LuTate	85	Yes	43	0.0002 <sup>d</sup>
Carboplatin/etoposide	104	Yes	50	<0.0001 <sup>d</sup>
Combination	141	Yes	85	0.0058 <sup>e</sup>

<sup>a</sup> Tumour growth inhibition was determined on day 18

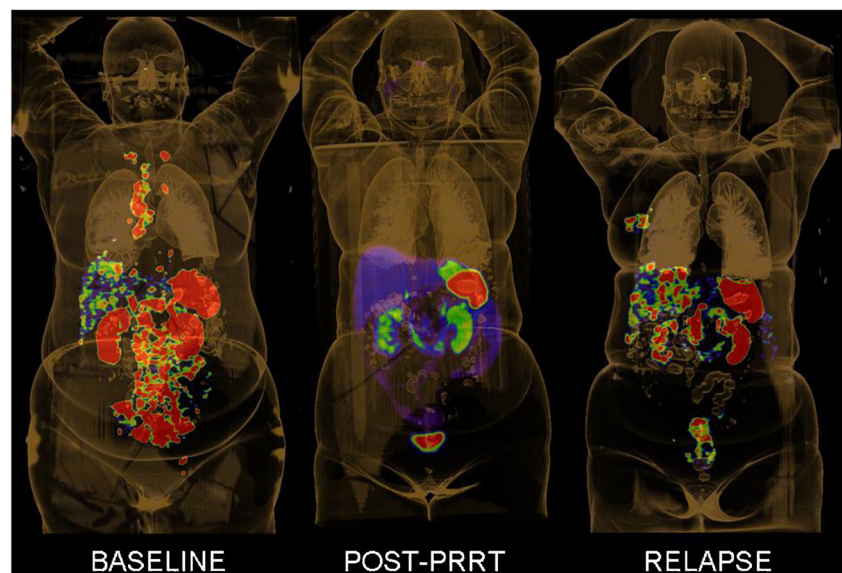
<sup>b</sup> ANOVA followed by Dunnett's post hoc test vs vehicle control

<sup>c</sup> Log-rank test: <sup>d</sup> vehicle vs therapy or <sup>e</sup> carboplatin/etoposide vs combination

3.7 GBq of Ytate along with an arginine and lysine amino acid infusion as a renoprotectant. In addition, the patient received 50 mg daily of oral etoposide as a radiosensitiser for 7 days, commencing 2 days prior to the infusion. Carboplatin use was not considered given her very poor renal function and the potential for additional myelosuppression.

Disease burden was reassessed with GaTate and FDG PET 1 month post-infusion and showed a near complete response to therapy, with the GaTate scan revealing a marked reduction in nodal size and most of the disease showing no residual GaTate activity. Similarly, the FDG PET/CT scan showed near complete metabolic response, with the only residual disease seen in a subcentimetre subcarinal lymph node. This corresponded to a 99 % reduction in the disease volume (from 2,394 ml to 20 ml), with a similar reduction seen on the FDG scan, reflecting a 2 log tumour cell kill. The patient's clinical response matched the radiological response with resolution of peripheral oedema and impaired renal function and reduction in opioid requirements. These changes were associated with an improvement of performance status from Eastern Cooperative Oncology Group (ECOG) 3 to ECOG 1.

**Fig. 3** GaTate PET/CT scans of the case study. Representative fused images are shown at baseline (*left panel*), complete metabolic response at 3 months (*middle panel*) and on progression (*right panel*)

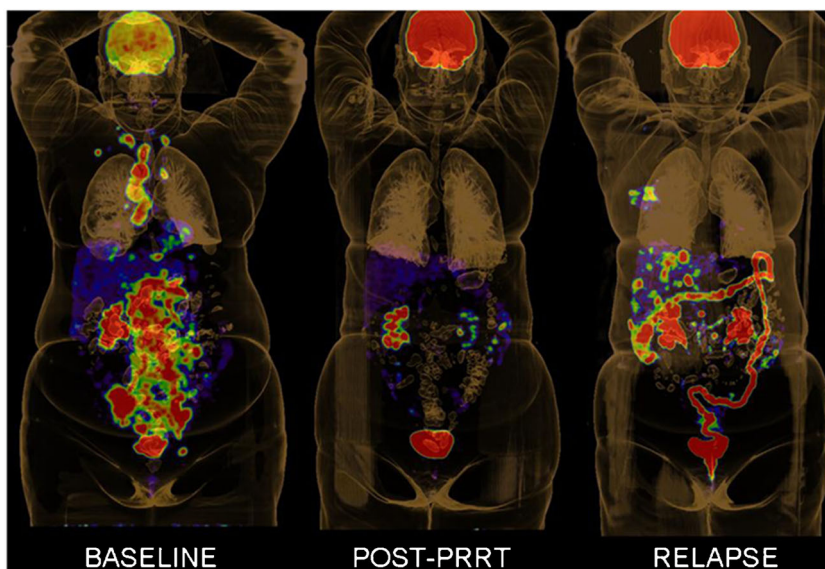


When a GaTate scan 2 weeks later revealed repopulation to a volume of 178 ml, the patient received a dose of LuTate combined with <sup>111</sup>In-DOTA-octreotate (InTate) with oral etoposide. These agents were chosen due to their shorter particle length, which improves crossfire effect in smaller lesions and maximises radiation delivery to individual SSTR-expressing cells. The patient received a subsequent dose of LuTate 1 month later and again achieved a complete metabolic response (Figs. 3 and 4, middle panel). The treatment was well tolerated apart from mild fatigue, nausea, symptomatic grade 2 anaemia requiring a red blood cell transfusion and grade 3 thrombocytopenia. Unfortunately, 4.5 months after the initial infusion, the patient developed progressive disease involving the liver, multiple nodal stations, pleura, bone and the right breast (Figs. 3 and 4, right panel). Taking into consideration the persistence of grade 3 thrombocytopenia with clinical and GaTate evidence of early disease recurrence, a decision was made not to re-treat with further PRCRT and the patient died shortly thereafter.

## Discussion

In this study, we employed preclinical models of SCLC to investigate the therapeutic potential of PRCRT. The preclinical findings demonstrate that PRCRT using LuTate in combination with carboplatin/etoposide is superior to either PRRT or chemotherapy alone in an SSTR2-expressing SCLC cell line. The potential of this therapy is supported by a clinical case, in which we demonstrated a complete metabolic response in a patient treated with PRCRT for a GaTate-avid SmCC. The limitations of this study include the fact that the preclinical model and clinical case received different chemosensitisation

**Fig. 4** FDG PET/CT scans of the case study. Representative fused images are shown at baseline (*left panel*), complete metabolic response at 3 months (*middle panel*) and on progression (*right panel*)



and radiopeptides. The small absolute but large relative volume of xenografts in a mouse compared to tumours in a human make testing radionuclides in the preclinical setting difficult to directly extrapolate to humans. Although  $^{90}\text{Y}$  has significant theoretical advantages in large and heterogeneous tumour burdens, such as that in our patient, due to a longer beta particle range in tissue than for  $^{177}\text{Lu}$ , this compromises dose delivery in small tumours and increases collateral radiation to adjacent body tissues. In the case of a xenograft measuring 8–9 mm, there is very significant crossfire irradiation of the body of the mouse and suboptimal microdosimetry to the tumour itself. With respect to the chemotherapy regimen, we tested the most common treatment of human small cell carcinoma, a platinum/etoposide doublet. In the patient, renal failure precluded use of the platinum agent and therefore we were only able to use etoposide. This is, however, a known radiosensitiser [26] and has single-agent efficacy in small cell carcinoma [27]. Thus, although different, we believe the human example is relevant to our preclinical testing and given the significant clinical and metabolic response seen by the patient, in the context of the limited options available for relapsed SmCC, we believe that this therapy warrants further evaluation.

The significant advantage of PRRT is that cells overexpressing SSTR2 will be targeted by an intravenous dose of the radiopeptide, irrespective of their anatomical location, meaning that patients whose disease is not limited to a tolerable external beam radiation field can be offered the potential synergistic effects of radiation and chemotherapy. Systemically delivered peptide, radiolabelled with a metal that undergoes continuous radioactive decay, ensures that every cell that undergoes cell division during the decay of the radiometal will be exposed to the toxic effects of the radioactive emission during a vulnerable phase of the cell cycle. This

may be of particular importance, given the high proliferative rate of SmCC.

Although SSTR2 overexpression in SCLC biopsies has been previously documented [6], trials evaluating long-acting somatostatin analogues have been disappointing. A trial of three times daily somatostatin analogue in patients with extensive SCLC failed to induce a response with a median time to progression of 44 days [28]. Others have demonstrated that the addition of somatostatin analogue therapy to chemotherapy in patients with documented SSTR expression (measured by  $^{111}\text{In}$ -octreotide scan) led to an improvement in time to progression and overall survival in patients with limited stage SCLC [29]. SSTR was overexpressed in 92 % of patients, and in 28 of 112 patients there was a reduction in the degree of SSTR expression (by 4–28 %) during the course of therapy, although this finding was not correlated with disease extent, response to therapy or survival. Although PRRT is routinely and successfully used for the treatment of SSTR-expressing neuroendocrine tumours [30], there are only limited and generally discouraging data in relapsed SmCC [14, 11, 15]. In a recent study, PRRT ( $^{177}\text{Lu}$  or  $^{90}\text{Y}$ ) was delivered for patients with high levels of semi-quantitative SSTR expression with a time for tumour progression of 90 days from the first dose of PRRT (range 7–238) with no clinical or objective responses seen [11]. The underlying reasons for these results are unclear and may relate to acquired radioresistance of heavily pretreated patients, heterogeneous uptake with discordant disease given lack of concurrent FDG uptake by PET, suboptimal dosing of PRRT or the lack of radiosensitising chemotherapy.

In our case study, oral etoposide was chosen because of its single-agent activity in SmCC and the additional theoretical advantage of being a known radiosensitiser [26]. A relatively low dose of 50 mg/day for 7 days was used to equal the

majority of the decay of  $^{90}\text{Y}$  as well as minimise haematological toxicity. Additionally, in the clinical case presented, a variety of PRRT agents were chosen for their unique radiobiological characteristics in tissue penetration and physical decay rates [31]. For example, YTate has theoretical advantages in treating large volume disease, particularly if there is heterogeneous expression of SSTR in subpopulations of cells, whereas LuTate more efficiently irradiates smaller and more homogeneous deposits. InTate emits Auger electrons, which have a range of approximately a single cell and therefore augment radiation delivery to microscopic disease foci without increasing toxicity to adjacent normal cells, but provides no crossfire effect.

Our experience with neuroendocrine tumours suggests that moderately and poorly differentiated tumours can contain subpopulations of cells that express SSTR to a variable extent and have variable levels of glycolytic metabolism, which reflect their biological aggressiveness. We postulate that, as a tumour that often demonstrates a degree of neuroendocrine differentiation, SmCC is also potentially comprised of cells of variable characteristics with respect to both SSTR expression and chemosensitivity. As such, PRRT may be a useful adjunct to chemotherapy treatment.

## Conclusion

This study has demonstrated the benefit of adding chemotherapy to PRRT in a preclinical xenograft model of SmCC with high SSTR2 expression. Our preclinical findings have been translated into clinical use in the patient case described, highlighting the promise of PRCRT as a novel therapeutic approach for patients with relapsed SmCC. Given our promising preclinical data and clinical case, a prospective trial investigating the role of PRCRT in the management of SmCC is underway.

**Acknowledgments** D. Neil Watkins and Rodney J. Hicks received financial support from the Victorian Cancer Agency.

**Conflicts of interest** None.

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