Selective use of Peptide Receptor Radionuclide Therapy following comparative imaging of Ga-68 DOTATATE PET/CT against I-131 MIBG scintigraphy in a small Asian cohort of Adult Neuroblastoma

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SUMMARY

Adult neuroblastoma (AN) is rare with an extremely poor prognosis. No standard therapy exists for this entity and treatment options are limited in recurrent or refractory disease. ^{131}I-MIBG has been used in combination with myeloablative therapy before autologous bone marrow transplantation or in a salvage therapy setting. However, myelotoxicity is a dose-limiting factor in heavily pre-treated patients and response is not always sustained. Somatostatin receptor scintigraphy and theranostics with radiolabelled somatostatin receptor analogues are becoming more commonplace with the recognition of these receptors in over 90% of neuroblastoma cells. We describe three AN patients assessed for somatostatin receptor status and the novel use of ^{177}Lu-based peptide recep-tor radionuclide therapy (PRRT) in two of them and a literature review.

INTRODUCTION

We describe the use of ^{68}Ga-DOTATATE PET/CT to evaluate disease in three adults with histologically-proven neuroblastoma, in a prospective trial approved by the SingHealth Central Institutional Review Board (CIRB 2016/DNMP/001). Written consent was obtained from all patients. Scans were read by two blinded Nuclear Medicine Physicians independently and findings graded on a visual scale and analyzed on a per lesion basis. Consensus agreement was reached whenever discrepancies arose. On the basis of scan findings, two patients subsequently underwent treatment with PRRT on a compassionate basis with tumour board approval.

CASE REPORT

Patient 1

The first patient was an 18-year-old female with high-risk metastatic retroperitoneal neuroblastoma. Staging [^{18}F]FDG PET/CT and ^{131}I-MIBG scans showed a large hypermetabolic retroperitoneal mass, left supraclavicular and retroperitoneal adenopathy with bony metastases. Histology of abdominal tumour showed poorly differentiated MYCN non-amplified neuroblastoma, with 11q deletion and *ATRX* loss. Bone marrow biopsy showed 80% involvement. ^{68}Ga-DOTATATE PET/CT showed more lesions than ^{131}I-MIBG scan (Figure 1). She received standard induction chemotherapy. MIBG scan showed partial response (Curie score from 26 to 20), and bone marrow involvement <5%. She continued with chemotherapy and high dose ^{131}I-MIBG therapy (15mCi/kg bw) followed by consolidation with autologous stem cell rescue and radiotherapy, then post-consolidation immunotherapy (dinutuximab beta) and isotretinoin. She had stable disease after ^{131}I-MIBG therapy (Curie score 20), and partial response after the consolidation and post-consolidation phase (Curie score reduced to 10). However, one month later, she developed new abdominal tumours. She underwent resection and salvage chemo-immunotherapy. Unfortunately she had further disease progression in the marrow. She underwent a second round of MIBG therapy (15mCi/kg bw) followed by haploidentical stem cell transplant and immunotherapy. Repeat ^{131}I-MIBG scan (Curie score 18) showed increased bone metastases and no tracer uptake on ^{68}Ga-DOTATATE PET/CT scan. Her performance status deteriorated, and she succumbed to disease 35 months from initial diagnosis.

Patient 2

The second patient was a 32-year-old male with high-risk metastatic retroperitoneal neuroblastoma. [^{18}F]FDG PET/CT scan showed hypermetabolic retroperitoneal tumour, lymphadenopathy and liver metastases. Histology confirmed *MYCN* amplified, ALK-positive neuroblastoma. Bone marrow showed 30-40% involvement. He received chemotherapy and [^{18}F]FDG PET/CT showed partial response. Bone marrow involvement improved to 5-10%. ^{131}I-MIBG scan showed uptake in abdominopelvic, left supraclavicular lymphadenopathy and hepatic metastases, but failed to show extensive bony metastases seen on ^{68}Ga-DOTATATE PET/CT. He underwent salvage high dose ^{131}I-MIBG (12mCi/kg bw) followed by autologous stem cell rescue. Post-treatment 131I-MIBG and [^{18}F]FDG PET/CT scans showed decreased size of adenopathy, while hepatic metastases remained MIBG-avid (Curie score remained 2). In addition to

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Table I: Patient age, stage of disease, tumour characteristics, ^{68}Ga-DOTATATE PET/CT and ^{131}I-MIBG scan differences, and survival outcomes

Patient No.	Age at diagnosis (yrs)	INRGSS Stage of disease at diagnosis	Tumour *MYCN* amplification	Tumour ALK positivity	Resection of primary tumour	Number of lesions on ^{68}Ga-DOTATATE PET vs ^{131}I-MIBG scan			^{68}Ga-DOTATATE PET Krenning score	^{131}I-MIBG scan Curie score	SUV$_{max}$ of primary lesion	SUVmax of most DOTATATE-avid metastatic lesion	% Bone marrow involvement peri-scan	Survival since diagnosis
						Scan time point	^{68}Ga-DOTATATE PET scan	^{131}I-MIBG scan						
1	18	M	No	No	Gross total resection	Staging	111	30	2	26	11.6	15.6	80	
						Post-induction	33	22	1	20	Resected	4.0	< 5	
						No paired ^{68}Ga-DOTA-TATE PET scan performed with Post-consolidation ^{131}I-MIBG scan								35
						Disease progression	0	N.A.*	0	18	Resected	None	Unknown	
2	32	M	Yes	Yes	Not performed	Staging	25	5	2	2	15.6	17.0	30-40	18
						Post-consolidation	29	3	3	2	20.6	15.9	5-10	
3	37	M	No	Yes	Gross total resection	Staging	41	1	3	0	11.7	15.3	60-70	19
						Post-consolidation	26	4	3	4	Resected	20.3	20-30	

INRGSS = International Neuroblastoma Risk Group Staging System
*Diffuse bone metastases which were not quantifiable as discrete lesions; better assessed with Curie score as a measure of proportion involvement.

these, ^{68}Ga-DOTATATE PET/CT also showed extensive bony disease. After extensive consultation and in view of limited stem cell support, he received PRRT (183.6 mCi ^{177}Lu-DOTATATE). However, five weeks after PRRT, [^{18}F]FDG PET/CT scan showed disease progression, with new intracranial metastases. He developed neutropenia and pneumonia, and died 2 weeks later.

Patient 3

This patient was a 37-year-old male with high-risk metastatic mediastinal neuroblasto-ma. [^{18}F]FDG PET/CT showed hypermetabolic right posterior mediastinal mass, supraclavicular adenopathy and bone metastases. Mediastinal mass biopsy revealed *MYCN* non-amplified ALK-positive neuroblastoma and bone marrow biopsy showed 60-70% involvement. ^{131}I-MIBG scan showed only faint uptake in the primary tumour. ^{68}Ga-DOTATATE PET showed tracer-avidity in all sites and more bony lesions than ^{131}I-MIBG scan (Figure 2). He underwent chemotherapy and resection of the primary tumour, followed by high dose chemotherapy with stem cell transplant and radiotherapy. Bone marrow involvement reduced to 20-30%. However, a few months later, there were new [^{18}F]FDG-avid bone lesions. Again, the ^{68}Ga-DOTATATE PET/CT detected more bone lesions than [^{18}F]FDG and ^{131}I-MIBG scans. Bone marrow biopsy showed 90% involvement. He received PRRT (163.7mCi of 177Lu-DOTATATE) and developed pancyt-openia 3 weeks later. [^{18}F]FDG PET/CT showed mixed response. Multidisciplinary consensus was that the cytopenias were more likely due to disease progression in the marrow. Salvage Alectinib therapy was given, but his pancytopenia worsened. Repeat [^{18}F]FDG PET/CT showed disease progression in liver and bone. He died a month later.

DISCUSSION

Adult neuroblastoma (AN) is exceedingly rare and carries an extremely poor prognosis. No standard therapy protocol exists for adults with neuroblastoma and treatment options for recurrent or refractory multifocal high-risk neuroblastoma are limited. Radionuclide therapy using ^{131}I-MIBG has been used in the salvage setting, either as a single modality or in combination with myeloablative stem cell transplantation. Upfront incorporation of ^{131}I-MIBG therapy into the high-risk neuroblastoma induction backbone is currently being studied by the Children's Oncology Group, as it was observed to be effective as neoadjuvant treatment in advanced neuroblastoma[1,2].

However, myelotoxicity is often dose-limiting, especially in heavily pretreated patients, and response often not sustained. There is therefore a need for development of other therapeutic options, particularly for those who have either failed ^{131}I-MIBG therapy or with low uptake of ^{131}I-MIBG. Somatostatin receptors (SSTRs), particularly subtype 2, found richly expressed in most neuroblastoma cells, raise the possibility of using radio-labelled somatostatin analogs for diagnostic imaging (^{68}Ga-DOTATATE PET/CT) and radionuclide therapy (PRRT) in neuroblastoma.

Although ^{123}I-MIBG remains recommended for imaging norepinephrine uptake, due to its unavailability, ^{131}I-MIBG was used instead. Patients 1 and 2 showed high uptake in DOTATATE and MIBG scans, hence both opted for MIBG therapy initially as this is the more established treatment. Patient 1 then had minimal somatostatin receptor uptake on re-staging scan and became ineligible for PRRT, highlighting a possible "flip-flop" phenomenon, while Patients 2 and 3 underwent PRRT later.

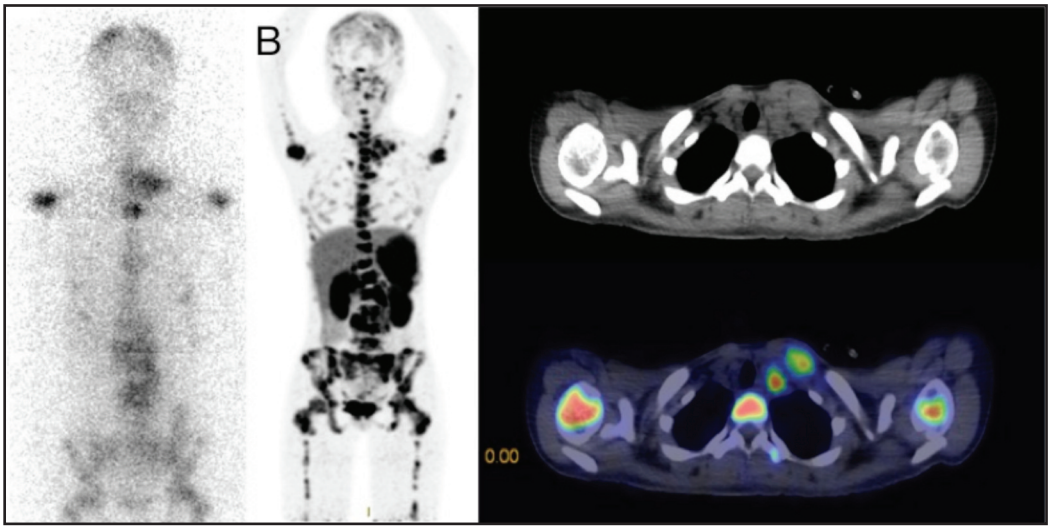

Fig. 1: Comparative imaging evaluation of extent of disease of Patient 1 at initial diagnosis. Anterior planar image of staging ^{131}I-MIBG scan (A), showing fewer lesions compared to maximal intensity projection image of ^{68}Ga-DOTATATE PET/CT (B); representative axial ^{68}Ga-DOTATATE PET/CT images of tracer-avid left supraclavicular adenopathy and bony lesions (C).

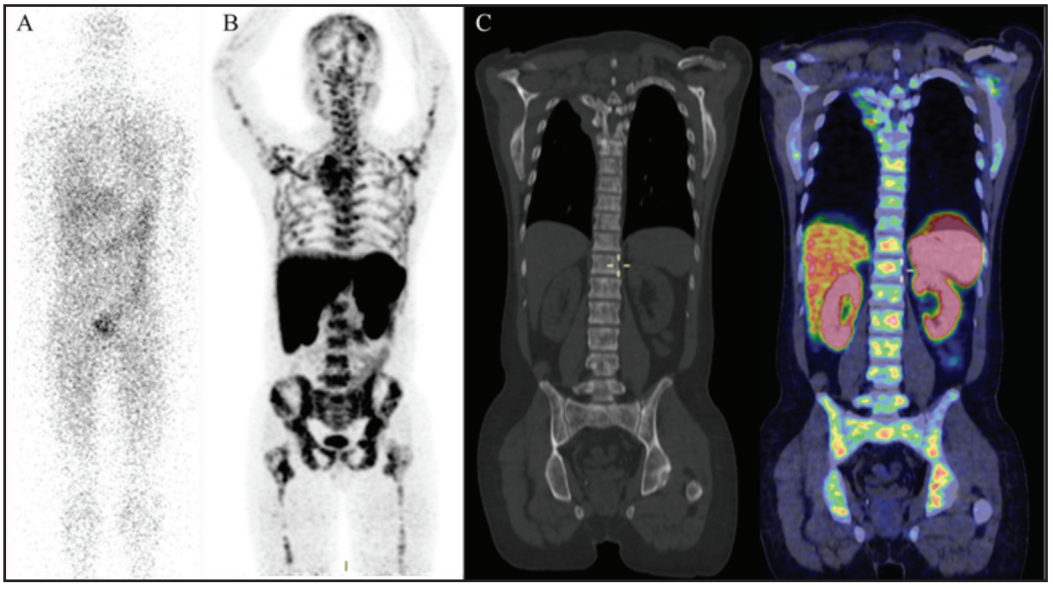

Fig. 2: Comparative imaging evaluation of extent of disease of Patient 3 at initial diagnosis. Anterior planar image of staging ^{131}I-MIBG scan (A), showing fewer lesions compared to maximal intensity projection image of ^{68}Ga-DOTATATE PET/CT (B); representative coronal ^{68}Ga-DOTATATE PET/CT images of tracer-avid bony lesions (C).

Patient 2 received ^{131}I-MIBG therapy initially with good effect. He opted for PRRT sub-sequently as bridging treatment before another ^{131}I-MIBG therapy due to limited autologous stem cell support. The basis for this approach was that PRRT may cause less myelotoxicity than ^{131}I-MIBG. This concept may suggest a new indication for PRRT in future: as an alternative or combinational therapy, reserving more myelotoxic MIBG therapy for later as salvage therapy.

Patient 3 had fewer lesions and faint uptake in MIBG compared with DOTATATE scan. Thus, after high dose chemotherapy and stem cell transplant, he received PRRT instead of ^{131}I-MIBG. The patients, stage of disease and tumour characteristics are shown in Table I.

The sensitivity of ^{68}Ga-DOTATATE PET/CT appeared superior to ^{131}I-MIBG scan on a per lesion basis in our series. This is attributable to PET's superior resolution over gamma imaging and the inferiority of iodine-131 compared to iodine-123.

Of our two PRRT patients, both developed pancytopenia within 6 weeks. While the temporal relation suggests PRRT-related myelotoxicity, both patients developed leukoerythroblastic picture and repeat imaging showed disease progression, suggesting the myelosuppression was in larger part due to disease than PRRT. However, we acknowledge the definite risk of myelotoxicity post-PRRT and long-term risks of mye-lodysplastic syndrome and acute

leukemia. Risk factors such as baseline cytopenia, bone metastases, multiple prior therapies, prior alkylating agents (e.g. Busulfan and Melphalan which our patients received) and radiotherapy increase risk and severity of post-PRRT myelotoxicity.[3] Dosimetry-based individualization of PRRT should continue to be explored, to achieve tumoricidal radiation dose to lesions without substantially increasing toxicity to healthy tissue.

One possible confounder for the poor survival of our 2 patients was the severity of their disease when given PRRT. Before PRRT, Patient 3 already had 90% bone marrow involvement while patient 2 had extensive liver and osseous disease. Moreover, these 2 patients already had high risk metastatic disease according to the International Neuroblastoma Risk Group Staging System, with additional poor prognostic factor of ALK positivity, and *MYCN* amplification.

Studies of ^{68}Ga-DOTA-conjugate imaging and PRRT in neuroblastoma

There are limited reports of somatostatin receptor imaging, and none of PRRT, in AN.

A case series comparing the ^{123}I-MIBG and ^{68}Ga-DOTATOC imaging in the diagnosis and staging of metastatic pheochromocytoma and neuroblastoma showed that amongst neuroblastoma patients (n=5), the sensitivities of ^{68}Ga-DOTATOC and ^{123}I- MIBG on a per-lesion basis was 97.2% and 90.7%, respectively.[4]

Two other case series successfully demonstrated that ^{68}Ga-DOTATATE can be used to image pediatric neuroblastoma and identify suitability for ^{177}Lu-DOTATATE PRRT, yielding response without significant toxicity.[5,6] Gains et al found that amongst 8 children with relapsed or refractory high-risk neuroblastoma, 6 had uptake on ^{68}Ga-DOTATATE PET/CT equal to or greater than the liver and received several administrations of ^{177}Lu-DOTATATE PRRT.[5] Kong et al compared ^{68}Ga-DOTATATE scans of 8 children with refractory neuroblastoma with their MIBG imaging. ^{68}Ga-DOTATATE PET showed additional disease in 3 of the 8 patients, and upstaged 1 patient by detecting marrow involvement. 5 patients had tissue samples available, and immunohistochemistry showed moderate or strong SSTR2 expression with an intensity score 3-4 on the ^{68}Ga-DOTATATE PET/CT. In 6 patients, ^{68}Ga-DOTATATE uptake was higher than background liver, 4 of whom were given PRRT on the grounds of progressive, symptomatic disease.[6]

In these studies, some ^{68}Ga-DOTATATE scans identified additional sites of disease not seen on MIBG imaging, suggesting ^{68}Ga-DOTATATE PET/CT may be more sensitive, and there might be an admixture of tumour cell populations expressing both norepinephrine transporters and somatostatin receptors. PRRT can potentially be used in combination with MIBG therapy to concomitantly target both types of neuroblastoma cells.

Role of ^{68}Ga-DOTATATE for prognostication

Despite differences between somatostatin receptor imaging and MIBG scans, there remains a potential prognosticating role for radiolabelled somatostatin analogs.

A clinicopathologic study showed that favorable histology neuroblastoma had significant positivity for SSTR1, SSTR2 and SSTR4, and expression of SSTR1 and SSTR4 was significantly higher in the surviving cases.[7] ^{68}Ga-DOTATATE radiopeptide has a predilection for SSTR2 receptors, hence its uptake implies higher SSTR2 density on neuroblastoma cells while no uptake may suggest other SSTR subtypes. It was previously shown that SSTR expression correlates well with survival, and neuroblastomas with unfavourable stage showed positive somatostatin receptor scans less frequently than tumours of more favourable stages, and *MYCN* amplification (associated with poorer prognosis) correlated with absent somatostatin receptor expression.[6,8-10]

Unexpectedly, our Patient 2 had unfavourable metastatic stage and *MYCN* amplification, yet positive somatostatin receptor scans. If larger studies find correlations between individual SSTR subtypes and survival, 68Ga-DOTATATE uptake can potentially be a novel prognostic marker for neuroblastoma.

Advantages of ^{68}Ga-DOTATATE imaging

Radiolabelled somatostatin analogue imaging has practical advantages over MIBG imaging as discussed by Alexander et al.[11] Firstly, plasma clearance is quicker with SSTR analogues (^{68}Ga-DOTATATE 2 hours, ^{123}I-MIBG 2 days), allowing injection and imaging to be done within 1 day rather than 2 days required for MIBG. Half-life of ^{68}Ga-DOTATATE is shorter than both ^{123}I-MIBG and ^{131}I-MIBG, time required for ^{68}Ga-DOTATATE PET/CT is about half that of MIBG scan. There is less patient preparation for DOTA-conjugated PET/CT than for MIBG scan (Lugol's solution to block free iodide uptake and avoidance of diet and medications that interfere with MIBG uptake). ^{68}Ga-DOTATATE also exposes patients to less radiation than ^{123}I-MIBG and [^{18}F]FDG PET.

CONCLUSION

Outcomes of AN are dismal. Treatment response to radionuclide therapies has been shown superior in older, compared to younger, neuroblastoma patients.[12] There are fewer systemic toxicities compared with conventional chemotherapy. While it is challenging to conduct randomized controlled trials on radionuclide therapies in high-risk neuroblastoma, more research is necessary to investigate: (i) the sensitivity and specificity of ^{68}Ga-DOTATATE PET/CT for staging, (ii) the potential use of PRRT earlier before multiple treatments compromise critical organ reserves, and (iii) combination therapy with MIBG, especially in patients where an admixture of tumour cells exists expressing either one of these receptors. Meanwhile, PRRT will remain at best an investigational or compassionate use salvage therapy option.

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