Targeted radiotherapy of neuroblastoma: Future directions

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Neuroblastoma is a malignancy predominantly of infancy. It originates most commonly in the adrenal gland and affects a hundred individuals per year in the UK. Half of neuroblastomas are highly aggressive, disseminated throughout the body of the patient and characterised by unresponsiveness to therapy or early relapse if remission is achieved. High-risk neuroblastoma is responsible for 12% of paediatric cancer fatalities and new treatments are urgently needed [1].

Ninety percent of neuroblastoma tumours express the noradrenaline transporter (NAT). These can be treated with targeted radiotherapy using an iodine-131-radiolabelled drug, meta-iodobenzylguanidine (¹³¹I-MIBG), which is structurally similar to noradrenaline. ¹³¹I-MIBG has produced long-term remission and palliation in patients with resistant disease [2]. However, some neuroblastoma tumours cease expression of NAT, engendering resistance to ¹³¹I-MIBG [2]. This observation prompted the diagnostic and therapeutic application of an alternative radiopharmaceutical – radiolabelled octreotate – which targets somatostatin receptors (SSTRs), expressed on human neuroblastoma cells [3-5].

Octreotate linked to the β-particle-emitting lutetium-177 (¹⁷⁷Lu-DOTATATE) binds with high affinity to SSTR2. The safe and successful treatment of children with neuroblastoma using ¹⁷⁷Lu-DOTATATE was recently reported [6,7].

The administration of both ¹³¹I-MIBG and ¹⁷⁷Lu-DOTATATE is expected to enhance therapeutic efficacy. Significantly, as the main unfavourable effect of ¹³¹I-MIBG therapy is myelosuppression whereas that of ¹⁷⁷Lu-DOTATATE therapy is renal toxicity, the combined treatment with ¹³¹I-MIBG and ¹⁷⁷Lu-DOTATATE is not expected to intensify adverse effects. In order for a clinical study of the combination of radiopharmaceuticals to proceed, the optimal sequence and timing of administration must be determined. Previous studies indicate that these factors have a profound influence on the efficacy of radionuclide therapy [8].

Following a study of patients with neuroblastoma, non-concordance between ¹²³I-MIBG- and ¹⁷⁷Lu-DOTATATE-derived images was reported [6], indicating variation between tumors with respect to capacity for radiopharmaceutical uptake. Significantly, it has been shown that the cellular uptake of both radiopharmaceuticals is enhanced by DNA-damaging agents, including ionizing radiation [9,10]. If such potentiation of receptor expression pertains also in vivo, the sequencing of administration of radiopharmaceuticals and the interval between injections could have a substantial influence on efficacy.

Radionuclide therapy delivers ionizing radiation at very low dose rate (LDR) (≤ 2 cGy/min), which decreases with time. The outcome of fractionated administration of ¹³¹I-MIBG and ¹⁷⁷Lu-DOTATATE cannot be predicted because it depends on the properties of the radionuclide and of the tumor [8,11-16] (Table 1). Therefore, experimental testing is required to determine the optimal scheduling of delivery of these two radiopharmaceuticals.

Two opposing outcomes of sequential administration of radiopharmaceuticals are envisaged: (i) prior exposure of tumour cells to one radiopharmaceutical could enhance the expression of the target of the subsequently applied radiopharmaceutical, engendering a positive therapeutic effect; and (ii) a priming dose of radiopharmaceutical may stimulate radioprotective (adaptive) responses in surviving cells thereby reducing the effectiveness of the subsequently delivered radiopharmaceutical. The establishment of the optimal schedule of delivery of radiopharmaceuticals will minimise the capacity of tumours, which do not succumb to initial radiopharmaceutical treatment, to develop resistance to subsequently administered radiotherapy.

Efforts to improve the therapeutic efficacy of targeted radiotherapy by combination with radiosensitisers are now being implemented. Furthermore, the reduction of resistance to targeted radiotherapy by means of combinations of radiopharmaceuticals which bind to alternative targets is likely to translate into the improvement of the management of patients with high-risk neuroblastoma.

Acknowledgements

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Table 1. Factors influencing the response to radionuclide therapy delivered at low dose and low dose rate.

<table>
<thead>
<tr>
<th>Factors that enhance cell kill</th>
<th>Factors that reduce cell kill</th>
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<tbody>
<tr>
<td>Radiation-induced bystander effect</td>
<td>Non-uniformity of tumour uptake of radiopharmaceuticals due to heterogeneity of target expression</td>
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<tr>
<td>Hypersensitivity to low-dose radiation</td>
<td>Increased radioresistance at low radiation dose</td>
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<tr>
<td>Radiation cross-fire</td>
<td>Adaptive response</td>
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<tr>
<td>Redistribution of cells to radiosensitive phases of the cell cycle and reoxygenation</td>
<td>Sustained repair of DNA damage during treatment</td>
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