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Commentary

Radiolabelled mIBG in the Treatment of Neuroblastoma

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ALTHOUGH THE outlook for children with neuroblastoma has improved in recent decades following the introduction of aggressive multi-agent chemotherapy [1], the prognosis remains poor. This is especially true for patients over the age of 1 year, those with advanced disease at presentation and those with biological markers of unfavourable disease, such as amplification of the oncogene *N-MYC* and chromosomal abnormalities such as 1p deletion. The introduction of new agents and improvement of existing treatments are essential if results are to be improved. One potentially valuable new agent is the catecholamine analogue meta-iodobenzylguanidine (mIBG) which can be labelled with a radionuclide, most commonly ^{131}I [2]. [^{131}I]meta-iodobenzylguanidine ([^{131}I]mIBG) is actively taken up by neuroblastoma cells in the majority of cases, and this provides an opportunity for selective irradiation of both the primary tumour and metastatic disease.

It is now 10 years since [^{131}I]mIBG was first employed in the treatment of neuroblastoma. This followed naturally from the use of [^{131}I]mIBG as a radiopharmaceutical for imaging of phaeochromocytoma [3] and neuroblastoma [4].

At a meeting in Rome in 1986, pioneers pooled their experience of [^{131}I]mIBG treatment in 75 patients, and its value as a palliative agent was immediately apparent [5–13]. An objective response or disease stabilisation was seen in 44 patients (59%) of whom 4 had complete remissions and 28 had partial remissions. These data must be interpreted cautiously, as the patient population was heterogeneous with regard to the extent of disease and prior treatment, [^{131}I]mIBG administration and dosimetry were not standardised, and the International Criteria for response assessment [14] had not yet been formulated. Yet, if nothing else, these results showed that some benefit may be expected in a heavily pretreated group of patients for whom conventional therapy offers little.

More recently, larger series of neuroblastoma patients showing varying response rates to [^{131}I]mIBG therapy, have been reported. In an Italian series of 31 heavily pretreated children with relapsed or refractory disease, two complete and three partial responses were seen (an overall response rate of 16%), while 15 patients had mixed responses or stable disease and 10 progressed [15]. In a series of 50 similar patients treated in Amsterdam, 7 patients had complete reponses and 22 had partial responses: an overall response rate of 58% [16]. Results of the United Kingdom Children's Cancer Study Group (UKCCSG) Phase I/II Study are intermediate between those of the Italian and Dutch series, with a response rate of 30% (confidence limits 10% to 50%) [17]. This study, involving eight British centres, included 25 patients with advanced, recurrent or resistant disease. It was designed to develop both a reproducible standard protocol for [^{131}I]mIGB administration and a reliable dosimetric system, and to correlate toxicity with whole body radiation dose received. In addition, uniform and conventional assessments of the effectiveness and toxicity of [^{131}I]mIBG were used. While many patients showed no objective tumour reduction, pain relief is often dramatic making non-curative treatment worthwhile [18].

These initial studies in an unfavourable population have shown that [^{131}I]mIBG has appreciable activity against neuroblastoma. It is exceptional for new drugs to produce complete responses in patients for whom all conventional treatment has failed. A higher response rate might reasonably be anticipated in untreated patients but, because of the heterogeneity of [^{131}I]mIBG uptake [19] and other factors, it seems unlikely that [^{131}I]mIBG would ever be curative if used as a single agent. Nonetheless, it is plausible that if such an active agent were to be added to established therapeutic regimens, more patients might be cured.

Two approaches to the incorporation of [^{131}I]mIBG into the standard treatment of neuroblastoma are being evaluated. After initial cytoreduction by chemotherapy and surgery, [^{131}I]mIBG may be used in an attempt to eradicate residual disease. For this purpose, it is added to "megatherapy" consolidation, that is, myeloablative high dose chemotherapy with or without total body irradiation supported by bone marrow transplantation or peripheral stem cell reinfusion. Alternatively, [^{131}I]mIBG may be used "upfront" as the initial treatment of newly diagnosed patients, prior to their receiving conventional chemotherapy. To appreciate the advantages and disadvantages of these different

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therapeutic strategies, it is first necessary to consider the theoretical background of [^{131}I]mIBG with particular regard to microdosimetry and radiobiology.

Targeted radiotherapy with [^{131}I]mIBG differs from most other treatments in several important respects. Firstly, the typical tumour cell receives most of its radiation dose from beta particles emitted by [^{131}I]mIBG taken up by neighbouring cells (within approximately a millimetre radius) rather than by its own uptake. Isolated cells receive less dose than clumps of cells and macroscopic tumours, at least in the idealised case of uniform uptake throughout the tumour. Of course, tumours have increasing cell number (as well as increasing heterogeneity of uptake) with increasing size and this eventually offsets the increasing cell kill which results from an increased absorbed dose. The result is a predicted "optimal cure size" for ^{131}I which is estimated to be close to 2 mm in the case of uniform uptake [20, 21], but less than this if microtumours experience size dependent uptake gradients due to restricted penetration of the targeting agent [22]. The important feature is that microscopic tumours are not necessarily more curable than slightly larger tumours, since dose absorption may be poorer. The lesser radiocurability of microtumours has been confirmed experimentally using multicellular tumour spheroids [23]. Moreover, [^{131}I]mIBG-targeted radiotherapy depends on active uptake by metabolically competent tumour cells; a viable tumour cell surrounded by metabolically dead tumour cells is dosimetrically equivalent to an isolated cell and would be less readily curable than the same cell in a viable clump. This feature of targeted radiotherapy contrasts with most other treatment modalities for which smaller tumours are almost always more curable than their larger counterparts. This is important when considering optimal sequencing of modalities in combined treatment strategies.

Another significant factor is acquired resistance: radiation resistance develops much less readily than chemoresistance and, although a mutation may lead to reduced cellular uptake of [^{131}I]mIBG, single cell mutants do not derive an automatic selection advantage from this because of cross-fire from neighbouring cells which have been successfully targeted. Clonal evolution of resistance to [^{131}I]mIBG will therefore occur less frequently than drug resistance.

Targeted radiotherapy delivers radiation in a complex time profile, although dose rates are inevitably low relative to external beam therapy. This means that even a single administration of targeted radiotherapy is protracted and similar in effect to fractionated external beam irradiation, and there is no radiobiological reason to fractionate it further.

Disseminated neuroblastoma means the co-existence of macroscopic tumours, subclinical metastases, cell clumps and single cells. Heterogeneous [^{131}I]mIBG uptake in larger tumours and poor dose absorption in tumour clumps and single cells are to be expected. With single agent [^{131}I]mIBG treatment, individual tumour cells and clusters significantly smaller than the optimal cure size may escape cure because of the microdosimetric disadvantage consequent on the path length of the radiation emitted by ^{131}I. At the other end of the tumour size spectrum, lumps of neuroblastoma are likely to evade cure because of heterogeneity of [^{131}I]mIBG distribution and the greater number of clonogenic cells. Mathematical model analysis demonstrates the superiority of combined modality treatment in this situation, with [^{131}I]mIBG used optimally to sterilise subclinical tumours in the millimetre size range, local modalities (surgery and limited external beam radiotherapy) to treat macroscopic tumours and systemic treatment (chemotherapy, total body irradiation) to eliminate microtumours and single cells [24].

Strategies of this type are beng evaluated in several centres. At the Royal Marsden Hospital, Surrey, [^{131}I]mIBG has been incorporated with high dose chemotherapy and bone marrow transplantation in patients with relapsed and refractory disease [25]. In Glasgow, 5 patients have been treated with a regimen combining [^{131}I]mIBG estimated to give a whole body radiation dose of 2 Gy, high dose melphalan and total body irradiation with bone marrow transplantation to overcome the myelotoxicity. Local external beam radiotherapy was also used in selected patients with a residual mass [26]. Early results demonstrate the feasibility of an approach which merits further evaluation. Use of peripheral blood stem cell support offers an alternative to bone marrow transplantation in patients treated with myeloablative schedules [27].

The special features of targeted radiotherapy already discussed have implications for sequencing of [^{131}I]mIBG and chemotherapy. Briefly, the early (upfront) administration of [^{131}I]mIBG maximises uptake and dose absorption in metabolically viable tumours of all sizes; induced regression results in smaller more accessible tumours containing fewer clonogenic cells (including fewer chemoresistant mutants); and there is an increased growth fraction in surviving repopulating cells. This is much better for chemotherapy application than the tumour state at initial presentation. If chemotherapy is given first, the malignancy for subsequent [^{131}I]mIBG treatment will include regressed and metabolically compromised tumours in which dose absorption is reduced. It is possible that agent access will be improved, as with chemotherapy, but this is unlikely to be a major consideration for subclinical tumours which are most in need of effective treatment by targeted radiotherapy [24]. These advantages and disadvantages of giving each agent first, when [^{131}I]mIBG and chemotherapy are both to be used, are summarised in Table 1. This provides a sound case for using targeted radiotherapy first.

The use of upfront targeted radiotherapy has been pioneered by the Amsterdam group [16, 28]. This approach has certain advantages, in addition to the theoretical benefits indicated above. In particular, the myelotoxicity of [^{131}I]mIBG, especially thrombocytopenia, is greatly reduced when it is given prior to chemotherapy. The Amsterdam strategy involves multiple administrations of [^{131}I]mIBG alone at moderate dose levels with long intervals—often several weeks—between each course, which is not theoretically optimal as it might be expected to facilitate the continued growth of micrometastases during and between treatments. However, the considerable clinical experience of this approach, demonstrates feasibility, and encourages the exploration of related approaches predicted to be advantageous.

The UKCCSG has just embarked upon a clinical pilot study which employs a single dose of [^{131}I]mIBG as the initial treatment, followed by conventional combination chemotherapy. It is a dose escalation study designed to find the maximum tolerated dose of [^{131}I]mIBG when used in this way without bone marrow support. If this approach proves to be feasible, it will probably become the experimental arm of a randomised trial comparing combined modality therapy with chemotherapy alone.

The use of [^{131}I]mIBG upfront does pose significant logistic difficulties and it will be important to streamline the process. In future, patients suitable for [^{131}I]mIBG therapy might be rapidly identifiable by PCR-based molecular methods, measuring the expression of the noradrenaline transporter gene [29], although

Table 1. *Comparative effects on tumour curability of alternative sequencing strategies for combined modality treatment using* [^{131}I]*mIBG and chemotherapy*

	Effect of first modality (either [^{131}I]mIBG or chemotherapy)	Curability by second modality: [^{131}I]mIBG	Curability by second modality: chemotherapy
Clonogen number	↓	↑	↑
Chemoresistant mutants	↓	—	↑
Agent penetration	↑	↑	↑
Proliferative fraction	↑	—	↑
Cellular metabolism	↓	↓	—
Radiation cross-fire	↓	↓	—

^{123}I or [^{131}I]mIBG scintigraphy may still be required for staging and pretherapy dosimetry.

Using [^{131}I]mIBG as part of the initial treatment of neuroblastoma and optimising its scheduling with other components of the therapeutic regimen are not the only ways in which results of [^{131}I]mIBG treatment might be improved. The commercially available radiopharmaceutical [^{131}I]mIBG is suboptimal for therapy as it is provided as a minority of radiolabelled molecules diluted by a vast excess of unlabelled molecules which will compete for cellular uptake and may confer unwanted effects. Several methods now exist for synthesis of high specific activity (no-carrier-added) [^{131}I]mIBG [30, 31] and experimental studies with this preparation suggest it is therapeutically superior [32, 33]. Large scale production of no-carrier-added [^{131}I]mIBG for therapeutic clinical use is awaited.

In summary, the last 10 years have seen an evolution in the role of [^{131}I]mIBG therapy. Initially, following the demonstration that it was an agent with activity against disseminated neuroblastoma, it was regarded as a rather sophisticated tool for palliation of symptoms in patients with end stage disease. Recently, it has been incorporated into combined modality regimens. Whether these regimens will improve the prospects of cure remains to be seen. Currently, a different formulation of this radiopharmaceutical, no-carrier-added [^{131}I]mIBG, is undergoing laboratory evaluation. If the promise of an improved tumour:normal tissue ratio (therapeutic ratio) is achieved, there is further hope for a better clinical outcome for children with advanced (stage) neuroblastoma.

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