Advances in the management of neuroblastoma have been made in several different areas over the last few years. Mass screening programmes have been developed for the detection of asymptomatic neuroblastoma in children under 2 years of age. These programmes are based on the measurement of urinary catecholamines. Prognosis has been related to histopathological grading, measurement of substances in serum such as serum ferritin and neuron-specific enolase, and amplification of n myc. Specific immunological markers have facilitated the diagnosis of minimal bone marrow disease and made differential diagnosis from other small round-cell tumours more reliable. Modest improvements in survival have been achieved by combinations of newer chemotherapy agents in induction programmes, and high-dose chemotherapy and autologous bone marrow transplantation as consolidation therapy (Appendix B). However, despite these advances, long-term survival remains poor in children over 1 year of age with widespread disease at diagnosis. Four-year disease-free survival in these children is only approximately 30%. New ways of approaching the therapy of neuroblastoma therefore clearly need to be devised in an attempt to improve the cure rates. Targetted radiotherapy with mIBG provides one such approach.

**General Principles**

Targetted radiotherapy using unsealed sources of radiation has been available since the 1940s; however, many questions are still outstanding. In order to eradicate a tumour and for the patient to survive, a high absorbed dose of radiation must be given to the tumour with a minimal dose to the normal tissues. To date, the only successful use of an unsealed radionuclide for therapeutic purposes has been confined to $^{131}$I in the treatment of thyroid carcinoma.

The protocols which have been employed for the use of this radionuclide are usually empirical. One method has been to give an initial activity of 3000 MBq (81 mCi) to ablate normal thyroid remnants, followed by subsequent treatment activities of 5550 MBq (150 mCi) to eradicate the differentiated thyroid carcinoma. Successive therapy activities of radio-iodine are given until the lesion is no longer visible on a radioisotope scintigram. However, because it is difficult to accurately measure the functioning volume of tumour it has not been possible to calculate the actual radiation dose being given to the lesion and thus discover the dose response of targetted radiotherapy in this disease.
Practical Aspects of Targetted Radiotherapy with mIBG

In practice, the level of absorbed radiation dose achieved by a tumour does not always correlate with its response to mIBG therapy. Tumours with apparently high uptake may show poor response, whilst tumours with low uptake may show very good response. This is probably due to a variety of factors, including the heterogeneity of the tumours, the variation in sensitivity of the imaging systems, and the variation of differentiation within the tumour. In the case of adults with differentiated thyroid carcinoma, these details are relatively less important since radioiodine that is not concentrated in the thyroid is rapidly excreted through the gastrointestinal tract and the kidneys. In contrast, however, for the child with neuroblastoma, it is important to estimate more accurately the dose received by the tumour and the whole body, since radiolabelled mIBG is also taken up by the vital organs in addition to the tumour; resulting in side effects, the most significant of which is bone marrow aplasia.

Principles of Therapy with mIBG

The ideal physical and biological properties of a radiopharmaceutical intended for therapy should be such that a large absorbed dose of radiation is received by the tumour with little or no dose to other tissues of the body. In general, radionuclides for therapy are chosen for their abundance of non-penetrating radiations (soft x and y rays, α, β−, β+, internal conversion and Auger electrons), and their lack of penetrating radiations (energetic x and γ rays). In this way, the radioisotope taken up by the tumour emits large quantities of non-penetrating radiations which deposit their energy in a very short tract, so that small tumours can be successfully treated.

In the case of mIBG, suitable isotopes of iodine are 131I, 125I and 124I. 131I has a half-life of 8 days and the most abundant of its wide range of β− emissions has a mean energy of 192 keV. 125I emits low-energy γ rays, as well as Auger electrons with mean energies of 1–30 keV; 124I is mainly a β+ emitter. 125I-mIBG may be a useful therapeutic agent in the future; it has a long half-life of 60.2 days, and if the 125I-mIBG is taken up adjacent to or in the cell nucleus, the very short path Auger electrons emitted may give a therapeutic effect limited to that cell over a longer time, sparing surrounding normal cells. Therapeutic activities of 124I-mIBG would be very expensive but the radiopharmaceutical may prove useful, delivering a high dose-rate over a shorter period of time (124I has a half-life of 4.2 days). At present only 131I-mIBG is used regularly for targetted radiotherapy in neuroblastoma, although 125I-mIBG has been used in a few centres. The relatively high-energy γ emissions of 131I are one of the reasons why it is not ideal for targetted radiotherapy, but these do facilitate imaging and dosimetry.

To gain maximum information from therapeutic mIBG, scintigraphic imaging of the patient after administration of the therapy activity should include techniques which can be used for the calculation of absorbed doses to normal tissues and to tumour. This will allow the derivation of optimum activities for administration to minimise damage to normal tissues, and the calculation of a tumour dose-response curve. The methods used for dosimetry estimation of radiiodine-labelled mIBG are outlined in Chapter 6.

Selection of Patients for mIBG Therapy

Many centres are using many different criteria for selection of patients for treatment with radiolabelled mIBG. In some, mIBG is reserved for those children who have failed all conventional treatment. In others it is used for those children who have minimal residual disease, whilst in yet others it is used early on in the course of treatment of their disease. In some centres it is used as a single agent, whilst in others it is used in combination with other treatment modalities. In all centres the patients who are offered mIBG therapy are very carefully selected. Patients who are expected to survive for less than two months should not be offered this treatment, unless it is being given for palliative purposes (in which case smaller activities should be considered). Patients who are acutely ill, requiring constant or frequent close-contact nursing, medical and parental care, should likewise not be offered this treatment, due to the radiation protection problems which would be encountered. Children whose bone marrow is heavily infiltrated with neuroblastoma, and who on mIBG scintigraphy show increased activity in the bone marrow, should not be offered mIBG therapy since bone marrow aplasia is a well-recognised side effect in these situations. Children with known disease which does not image with tracer activities of radiolabelled mIBG are not eligible for therapy in some centres in the United Kingdom.