Pergamon

European Journal of Cancer Vol. 31A, No. 2, pp. 252–256, 1995

0959-8049/95 $9.50+0.00

0959-8049(94)E0036-4

Multi-modality Megatherapy with [^{131}I]Meta-iodobenzylguanidine, High Dose Melphalan and Total Body Irradiation with Bone Marrow Rescue: Feasibility Study of a New Strategy for Advanced Neuroblastoma

M.N. Gaze, T.E. Wheldon, J.A. O'Donoghue, T.E. Hilditch, S.G. McNee, E. Simpson and A. Barrett

New therapeutic approaches are needed for advanced neuroblastoma as few patients are currently curable. We describe an innovative strategy combining [^{131}I]meta-iodobenzylguanidine ([^{131}I]mIBG) therapy with high dose chemotherapy and total body irradiation. The aim of combining these treatments is to overcome the specific limitations of each when used alone to maximise killing of neuroblastoma cells. Five children received combined therapy with [^{131}I]mIBG followed by high dose melphalan and fractionated total body irradiation. Autologous bone marrow transplantation was undertaken in 3 patients and allogeneic in 2 patients. One patient received additional localised radiotherapy to residual bulk disease. One patient is alive without relapse 32 months after treatment. 4 patients relapsed after remissions of 9, 10, 14 and 21 months. These results indicate that this combined modality approach is feasible and safe, but further evaluation is necessary to establish whether it has advantages over conventional megatherapy using melphalan alone.

Key words: bone marrow transplantation, combined modality therapy, [^{131}I]meta-iodobenzylguanidine, neuroblastoma, melphalan, radioisotopes, whole body irradiation
Eur J Cancer, Vol. 31A, No. 2, pp. 252–256, 1995

INTRODUCTION

TREATMENT OF advanced neuroblastoma remains unsatisfactory. The standard treatment of combination chemotherapy followed by surgery induces a complete remission in about 40% of cases, yet more than half subsequently relapse, and the long term survival rates at best are less than 20%. It is to improve results in this group of patients that intensive treatment protocols, referred to as 'megatherapy', which combine high dose chemotherapy and/or total body irradiation (TBI) with autologous bone marrow transplantation (BMT) have been developed [1, 2].

Targeted radionuclide therapy with [^{131}I]meta-iodobenzylguanidine ([^{131}I]mIBG), a catecholamine analogue selectively taken up by cells of neural crest origin, was first used for the treatment of neuroblastoma following the demonstration that, like phaeochromocytoma, it could be imaged by this radiopharmaceutical. In patients with relapsed or refractory disease, for whom all conventional treatments had been exhausted, response rates of up to 58% have been reported [3, 4]. These results have encouraged evaluation of earlier [^{131}I]mIBG treatment [3].

In conventional cancer therapy, smaller tumours are easier to eradicate than larger ones, largely because they contain fewer clonogenic cells. By contrast, micrometastases smaller than about 1 mm diameter are predicted to be more difficult to cure with [^{131}I]mIBG therapy [5, 6]. This is because radionuclide disintegration energy is absorbed inefficiently in microtumours whose diameter is less than the mean range of the ^{131}I beta particles, about 600 μm. This hypothesis has recently been supported by experimental evidence using neuroblastoma spher-

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Revised 6 Dec. 1993; accepted 21 Jan. 1994.

oids [7]. Targeted radionuclide therapy using [^{131}I]mIBG is most likely to cure tumours of about 2 mm diameter [6]. The likelihood of cure is reduced below this optimal size by the physical characteristics of ^{131}I beta particles and above this size by the greater number of clonogenic cells.

The use of [^{131}I]mIBG in combination with other treatments which are effective outside its optimal size range is predicted to overcome this limitation [8]. The efficacy of TBI is limited by the maximum dose which can be tolerated. Tumours up to about 1 mm diameter are likely to be cured by TBI, whereas larger deposits will contain too many clonogenic cells for eradication. Tumour masses greater than about 1 cm may be revealed by modern imaging techniques, and can be treated by localised, high dose external beam radiotherapy.

Figure 1 shows the relationship between tumour size and the number of clonogenic cells killed, assuming typical values for the radiosensitivity of neuroblastoma [8]. TBI to a total dose of 14 Gy is predicted to achieve a log cell kill of 6, which is likely to eradicate micrometastases less than 1 mm diameter. Tumour deposits greater than 1 cm diameter will be sterilised if they are detected by imaging and treated by local radiotherapy. Tumour deposits of intermediate size which are too large for cure by TBI and too small to be detected by imaging may, therefore, lead to failure of treatment using a combination of TBI and local radiotherapy. [^{131}I]mIBG, with its optimum cure size measured in millimetres, used in addition to TBI and local radiotherapy may increase the chance of eradicating all tumour deposits, and thus make patient cure more likely.

Here we report a pilot study of multi-modality megatherapy, aimed to maximise killing of neuroblastoma cells. [^{131}I]mIBG targeted radiotherapy, which gives a degree of tumour selectivity, was combined with external beam TBI and high dose melphalan, to offset the limitations of [^{131}I]mIBG therapy in smaller micrometastases, and localised external beam radiotherapy for large, measurable deposits. BMT was used to circumvent fatal myelotoxicity.

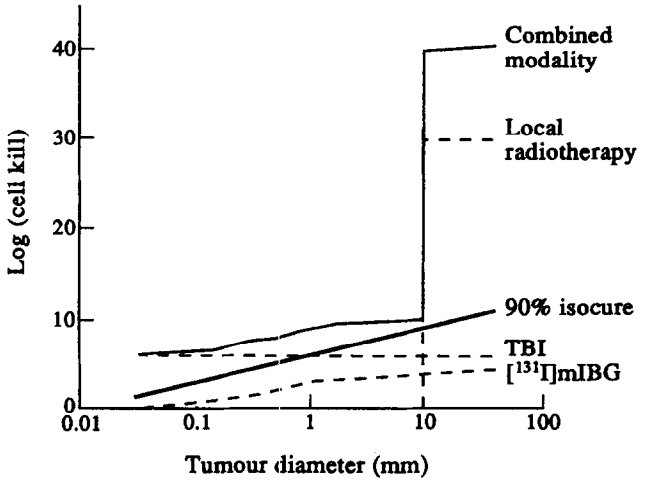

Figure 1. The log cell kill (i.e. -log survival) required for a 90% probability of cure for neuroblastoma tumours of different sizes is shown by the straight, thick line, assuming typical parameters for neuroblastoma cells. For tumours of a particular size, a value for log cell kill which falls above this line is likely to be curative, whereas cure is unlikely if the value falls below the line. Broken lines show the log cell kills achieved with total body irradiation alone (limited and, therefore, likely to be ineffective for tumours greater than 1 mm diameter), [^{131}I]mIBG alone (less effective in tumours less than 2 mm diameter), and local radiotherapy alone (restricted to detectable tumours greater than about 1 cm diameter). The continuous line shows the calculated log cell kill for combined modality therapy. As this is above the 90% isocure line at all tumour sizes, a high likelihood of cure is achieved.

PATIENTS AND METHODS

5 patients, 4 boys and 1 girl, aged from 3 to 11 years, with advanced (International Neuroblastoma Staging System [9], stage 4) disease were treated with multi-modality megatherapy following initial chemotherapy and surgery. This was for "consolidation" in 3 patients in clinical complete remission or with the aim of ablating known residual or recurrent disease in 2 patients. Patient data are summarised in Table 1. Details of each patient's initial treatment and disease status at the time of megatherapy are as follows:

Patient 1

Induction chemotherapy with six courses of OPEC (vincristine, cisplatin, etoposide and cyclophosphamide) followed by surgery to the primary tumour. Following relapse, he received radiotherapy to disease in the neck and three courses of carboplatin. In clinical complete remission at the time of megatherapy.

Patient 2

After six courses of OJEC (vincristine, carboplatin, etoposide and cyclophosphamide), there was residual bone marrow disease, which was cleared by two courses of OPEC. Bone marrow harvest and surgery to the primary tumour were followed by a further course of OPEC as there was a delay in arranging megatherapy. Bone marrow prior to megatherapy showed relapse, i.e. progressive disease at the time of megatherapy.

Patient 3

Induction chemotherapy with rapid COJEC (high dose intensity vincristine, carboplatin, cisplatin, etoposide and cyclophosphamide within the European Neuroblastoma Study Group Trial 5). Full doses were given but there was a 2-week delay during treatment of a fungal chest infection. After surgery there was a residual mass, but there had been an 80% reduction from the presenting size, i.e. partial response at the time of megatherapy.

Patient 4

Induction chemotherapy was with 12 courses of vincristine, ifosfamide, etoposide, carboplatin and epirubicin. Following relapse, he had a complete response to a further 14 courses of the same regimen, and was in clinical complete remission at the time of megatherapy.

Patient 5

Following removal of a small primary tumour, he received rapid COJEC with no delays or dose modifications. As he had residual bone marrow disease and poor renal function on completion of rapid COJEC, he was given 6 months of oral etoposide which lead to clearance of the bone marrow disease and permitted recovery of renal function. He was in complete remission at the time of megatherapy.

Bone marrow had been shown to be free of involvement by histology and immunohistochemistry at the time of harvest in the 3 patients for whom autologous BMT was to be used. Ideally, scintigraphy had shown that the tumour took up [^{131}I]mIBG, but patients in whom this investigation had not been performed,

Table 1. Patients' characteristics and results of treatment

	Patients				
	1	2	3	4	5
Age (years)	6	3	5	11	10
Sex	Male	Male	Female	Male	Male
INSS stage [9] at presentation	4	4	4	4	4
INSS disease status [9] at time of treatment	In second remission.CR	Isolated bone marrow relapse. PD	Residual abdominal mass.PR	In second remission. CR	In first remission. CR
Diagnostic mIBG scans	Positive	Positive	Positive	Negative (done only in remission)	Positive
Administered activity of [^{131}I]mIBG (GBq)	8.25	9.25	6.63	10.25	9.60
Whole body absorbed dose of [^{131}I]mIBG (Gy)	1.68	1.54	1.62	2.09	1.92
TBI dose (Gy)	14.40	12.60	12.96	12.60	12.60
Fractionation	8 F in 4 days	7 F in 4 days	8 F in 4 days	7 F in 4 days	7 F in 4 days
Combined radiation dose (Gy)	16.08	14.14	14.58	14.69	14.52
Projected body radioactivity at 15 days (MBq)	7	20	<20	50 (some in bowel)	<30
Dose rate at 15 days (mGy/h)	0.06	0.19	<0.15	0.23	<0.17
Bone marrow transplant	Allograft	Autograft	Autograft	Autograft	Allograft
Days in hospital after BMT	24	33	50	99	95
Platelet dependent (days)	47	48	168	106	109
Days to WCC>1 × 10^9/l	28	20	87	25	75
INSS disease status [9] 6 months after megatherapy	CR	CR	PR	CR	CR
Status now	Dead from disease	Dead from disease	Alive with residual abdominal mass	Alive disease-free	Dead from disease
Time in remission (months)	10	14	32+	21	9
Survival (months)	23	15	32+	30+	10

CR, complete response; PD, progressive disease; PR, partial response; TBI, total body irradiation; F, fractions; BMT, bone marrow transplantation; WCC, white cell count; INSS, International Neuroblastoma Staging System.

or in whom it was negative at a time when they had no bulk disease, were also considered eligible. This was because most patients with neuroblastoma do exhibit uptake of [^{131}I]mIBG, and its use even in a patient without uptake would still exert a therapeutic effect through the non-specific whole body irradiation it caused, and so would not be "wasted". Informed parental consent was obtained in each case.

Prior to treatment, baseline endocrine, renal, cardiac and pulmonary function tests were performed. Iliac crest bone marrow was harvested under general anaesthesia from the patient and stored. No purging procedure was used. Even if allogeneic transplantation was planned, back-up marrow was obtained from the patient. Oral potassium iodide was administered to prevent thyroid uptake of free radioiodine.

A quantity of [^{131}I]mIBG, obtained from Amersham International (Little Chalfont, U.K.), estimated to give a whole body absorbed radiation dose of about 2 Gy [10], was administered via a Hickman central venous catheter over approximately 1 h on day 0. Intravenous hydration, sedation and anti-emetics were given as required. Whole body retention of ^{131}I (necessary for whole body dosimetry) was determined by monitoring the dose rate at 1.25 m from the patient. Scintigraphy was carried out on days 2, 5 and 9 for whole body dosimetry and to determine sites of [^{131}I]mIBG accumulation. On day 10, melphalan, 140 mg/m^2 was administered. On days 12–15, TBI was given. Our standard TBI protocol is eight 1.8 Gy fractions, totalling 14.4 Gy (maximum lung dose), twice daily at least 6 h apart, over 4 days using a cobalt-60 teletherapy unit without lung shielding [11]. However, because of the whole body radiation dose from [^{131}I]mIBG, approximately 2 Gy (Table 1), one fraction was omitted in 4 patients giving a total of 12.6 Gy in seven fractions. Marrow was re-infused via the Hickman line following the completion of radiotherapy. Full supportive care, including anti-bacterial, anti-fungal and anti-viral chemotherapy, blood products and parenteral nutrition was given as required.

As tumours larger than a centimetre or so diameter are unlikely to be sterilised by the radiation doses achievable with either TBI or [^{131}I]mIBG [8], localised external beam radiotherapy was also given to the residual abdominal tumour mass in Patient 3 following haematological recovery. Her tumour received 5.20 Gy from [^{131}I]mIBG, 12.10 Gy from TBI and 23.40 Gy local radiotherapy in 13 fractions over 17 days, resulting in a total tumour dose of 40.70 Gy. Additional radiotherapy was not given to the mass detected in Patient 1, as this showed exceptionally high [^{131}I]mIBG uptake, and the calculated total radiation dose, 58 Gy, was deemed adequate.

RESULTS

The combined treatment was generally well tolerated, and there was no early mortality. The principal toxicity was haematological, detailed in Table 1. The speed of engraftment was variable, although none failed to engraft. Initial treatment in Patients 3 and 5 was a high dose intensity chemotherapy regimen (rapid COJEC), the myelotoxicity of which, perhaps involving marrow stromal cells as well as stem cells, might in part account for the delay in haemopoietic recovery. Patient 4 had also been heavily pretreated. The delayed haemopoietic recovery in Patient 5 is also explained by the treatment he required for graft versus host disease.

It is unlikely that residual [^{131}I]mIBG at the time of transplantation contributed to delayed haemopoietic recovery, as projected body activity at 15 days (derived from serial measurements taken up to 9 days after administration) indicated that the remaining dose at this time (Table 1) was of the order of 0.2% of the administered dose (median 20 MBq), the same as a diagnostic dose. At these later times, more than 20% of body activity is in the liver and reducing with a half life of not more than 3 days.

All patients experienced a severe mucosal reaction which necessitated a period of total parenteral nutrition. One patient developed a brisk but self-limiting cutaneous erythema during TBI. All patients had infective complications. Clinical grade 2 graft versus host disease (skin 4+, liver 1+) was seen in Patient 5, who received allogeneic marrow without T cell depletion.

Two factors, in addition to delayed haematological recovery, led to the length of time spent in hospital being significantly longer than the European average (about 25 days) for Patients 3, 4 and 5. Patients 3 and 4 were not local but lived hundreds of miles away from the treatment centre. Graft versus host disease and complications of its treatment contributed to the duration of hospital stay in Patient 5.

Results of radiation dosimetry are shown in Table 1. In all patients, including those in clinical remission and the patient in whom [^{131}I]mIBG scintigraphy was negative, areas of disease were shown by scanning following [^{131}I]mIBG administration. Sites of [^{131}I]mIBG accumulation, in addition to the normal physiological concentration seen in the liver, myocardium, salivary glands and bladder were as follows: Patient 1: left sided abdominal tumour, just below the spleen; Patient 2: a small lesion in the right upper thigh; Patient 3: tumour uptake just off the midline on the left side of the abdomen level with the centre of the liver; Patient 4: small lesion on left side of mid-abdomen; Patient 5: small lesion on left side of upper abdomen and others just above the knee in the right leg, and in the right clavicle.

In 2 patients with measurable disease, calculated tumour doses of 44 Gy (Patient 1) and 5.2 Gy (Patient 3) were delivered by the mIBG component, in addition to that received from TBI.

DISCUSSION

Neuroblastoma is a radiosensitive tumour, and radiotherapy in the form of local external beam treatment [12], TBI with BMT [2] and targeted radiotherapy with [^{131}I]mIBG [3, 4] are all effective. The present strategy of combining TBI, local radiotherapy and melphalan with [^{131}I]mIBG was designed to overcome the theoretical disadvantages of using [^{131}I]mIBG alone. Early experience of [^{131}I]mIBG in combination with high dose chemotherapy and bone marrow rescue has been reported from the Royal Marsden Hospital (U.K.) [13].

The first aim of this study was to see whether these treatments, each with their own toxicities, could be combined safely without unacceptable treatment-related morbidity. Given that conventional megatherapy for neuroblastoma carries a mortality greater than 10% [2], our experience indicates that multi-modality megatherapy is safe, and the inevitable acute toxicity is tolerable, given full supportive care. Further follow-up is necessary before late morbidity can be assessed.

It is not possible to evaluate the efficacy of this strategy in such a small number of patients, and clearly more patients must be studied. Two facts, however, indicate that a high degree of cell kill has been achieved with this treatment. The time to relapse in Patient 1, at 10 months, greatly exceeds the duration of his previous remission (4 months). Patient 2 experienced a long remission (14 months) but died from rapidly progressive intracranial and spinal disease, with no overt disease outside the neuraxis. This suggests that perhaps the central nervous system acted as a sanctuary site, as was commonly seen following the introduction of effective systemic therapy for leukaemia, before the need for central nervous system prophylaxis was appreciated.

Clearly, when treatments are combined, the relative proportions of each are important. Mathematical studies suggest that killing of neuroblastoma deposits will be greatest when the whole body dose from the targeted component is 4 Gy, rather than the 2 Gy we have used [14]. [^{131}I]mIBG dose escalation should, therefore, be attempted, with corresponding reduction of the TBI component.

This is the first report of multi-modality megatherapy incorporating [^{131}I]mIBG, localised radiotherapy and TBI in a schedule with high dose chemotherapy and bone marrow rescue for advanced neuroblastoma. If further experience with this regimen confirms its tolerability, it is intended that it will be incorporated into a randomised multicentre clinical trial to assess its efficacy.

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Pergamon

European Journal of Cancer Vol. 31A, No. 2, pp. 256–261, 1995
Elsevier Science Ltd
Printed in Great Britain
0959–8049/95 $9.50+0.00

0959-8049(94)00509-5

A New ^{123}I-MIBG Whole Body Scan Scoring Method—Application to the Prediction of the Response of Metastases to Induction Chemotherapy in Stage IV Neuroblastoma

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A new semi-quantitative scoring system is proposed, especially designed for the comparative interpretation of sequential whole-body meta-iodo-benzyl-guanidine (MIBG) scans in stage IV neuroblastoma children. This method was applied to assess whether MIBG scan at mid-course of induction chemotherapy could predict the final response. 27 newly diagnosed children were investigated by three sequential ^{123}I-MIBG scans performed at the beginning, at mid-course (6 weeks) and at the end of neoadjuvant chemotherapy (12 weeks). Whole body scans were divided into nine regions in which the extension of bone metastases was separately quoted (score range: 0–3). The overall absolute scores were obtained by adding the scores of the nine regions. Relative scores were calculated by dividing the absolute score at each time by the corresponding pretreatment score. The score at mid-induction correctly predicted the overall response of metastases at the end of induction ($P < 0.0001$) in most cases. This method is easy to use, reproducible, subject to little inter-investigator variation, and thus well adapted to multicentric trials.

Key words: MIBG, scintigraphy, neuroblastoma stage IV, induction chemotherapy, scoring method
Eur J Cancer, Vol. 31A, No. 2, pp. 256–261, 1995

INTRODUCTION

NEUROBLASTOMA is one of the most frequent solid tumours in childhood. Most cases are diagnosed before the age of 5 years, with 50% occurring before the second birthday. Approximately 90 new cases are observed in France every year. The tumour is heterogeneous regarding its clinical features and evolution. Although the prognosis is favourable in localised neuroblastoma, the situation is quite different in metastatic tumours to bone (60% at the time of diagnosis). In spite of significant progress in paediatric oncology, metastatic neuroblastoma in children over 1 year of age remains a serious challenge. The prognosis has not been markedly improved over the last decade in patients with bone or bone marrow involvement. Treatment includes pre-operative induction chemotherapy, surgery, postoperative high dose chemotherapy (with or without total body irradiation), and autologous bone marrow transplantation.

^{123}I-MIBG is now considered as a first line method for the staging and follow-up of neuroblastoma [1–7]. However, a major problem is the lack of any reliable and precise scoring system to evaluate the bone response to therapy on MIBG scans. Some attempts based on the intensity of uptake have been proposed during the last decade in healthy adults [8] and in children with neuroblastoma [2], but do not seem to be used in multicentric

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Revised 15 Nov. 1994; accepted 25 Nov. 1994.