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First Line Targeted Radiotherapy, A New Concept in the Treatment of Advanced Stage Neuroblastoma

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33 previously untreated advanced stage neuroblastoma patients were treated with [^{131}I] meta-iodobenzylguanidine (MIBG). The number of treatments varied between 2 and 7 per patient (mean 3). Toxicity was seldom severe. Only thrombocytopenia WHO-grade 4 was noticed. Response was documented before surgery for the primary tumour was performed. There was one complete response (CR), 18 partial responses (PR), 11 had stable disease (SD) and 3 had progressive disease (PD). After MIBG therapy and surgery, 12 of 33 patients achieved a CR. This approach is feasible, comparable to multidrug chemotherapy in efficacy and less toxic. Long term results are not known yet.

Key words: [^{131}I] meta-iodobenzylguanidine, neuroblastoma, targeted radiotherapy, paediatric
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INTRODUCTION

In 1967, Morales and associates [1] first demonstrated that C-14-labelled epinephrine and its precursors concentrated in the adrenal medulla. In the first human studies with [^{131}I]MIBG (meta-iodobenzylguanidine) in 1981 Sisson and associates [2] demonstrated successful detection of phaeochromocytoma with this radiopharmaceutical in 8 patients. The growing interest in targeting of therapeutic radiation and the already existing experience with MIBG for diagnosis and treatment of phaeochromocytoma led to its use in neuroblastoma [3, 4].

At The Netherlands Cancer Institute (1264) total body scintigrams in 418 patients with neural crest tumours have been made. [^{131}I]MIBG correctly demonstrated primary, residual and recurrent tumour, as well as diffuse bone marrow infiltration, skeletal, lymph node and soft tissue metastases [5]. 140 of these patients have subsequently received therapeutic doses of [^{131}I]MIBG. Although the exact mechanism of uptake of [^{131}I]MIBG remains unclear, it is believed to share the uptake and storage mechanism with norepinephrine, in two ways: a sodium-dependent system with a high affinity but low capacity, which is easily saturable, and a sodium-independent, apparently unsaturable process of passive diffusion [6]. Unlike norepinephrine, MIBG is not metabolised and is excreted unaltered via the kidneys. 70–90% of the administered activity is recovered in the urine within 4 days.

Since early 1984, treatment with [^{131}I]MIBG was given to patients with progressive, chemotherapy-resistant disease to achieve palliation [7, 8]. After some time, a second group of patients was included, namely those with residual disease after chemotherapy and surgery. In this group there has already been a curative intention. The results in these patients were

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encouraging with regard to the palliative ability as well as response and survival rates. It became clear, however, that the most prominent responses were obtained in patients with a large tumour burden at the time of treatment. This finding has served as the basis for our study, the objectives of which were to document response in untreated children, and to further characterise the side-effects of MIBG treatment.

PATIENTS AND METHODS

33 patients were entered into the study between January 1990 and June 1994. There were 15 girls and 18 boys. Their age ranged from 6 months to 16 years. 5 children were under the age of 1 year at diagnosis. Homovanillic acid (HVA) and Vanillylmandelic acid (VMA) concentrations were elevated in all patients.

Serum ferritin concentration was increased in 23 cases, normal in 7 and unknown in 3. Lactate dehydrogenase (LDH) plasma levels were increased in 25 cases, normal in 4 and unknown in 4 patients. The primary tumour was located in the abdomen in 25 patients, in the thorax in 4 patients and in the pelvis in 3 patients. In one patient, there were multiple abdominal and also scrotal localisations. In 12 patients, lymph nodes were involved, regional in 5 and distant in 7 patients.

A tumour biopsy was taken in all patients to obtain an adequate tissue specimen for biological studies. Regarding *MYCN* amplification, more than 3 copies were found in tumour tissue of 7 patients. 25 patients had less than 3 copies. In 1 patient the test was not done. 18 tumours were diploid (DNA-index (DI) $\leq$ 1.2), 10 were triploid (DI 1.2–1.8) and 3 were tetraploid (DI 1.8–2.2). In 2, the results are not known. Loss of heterozygosity (LOH) of chromosome 1p36 was demonstrated in 11 of these tumours. In 21 there was no LOH 1p36 and in one tumour the result is not known.

During the operation for a tumour biopsy, bone marrow aspiration and trephine biopsies from both iliac crests were performed. These were positive at least on one side in 18 cases at diagnosis. Bone [^{131}I]MIBG or [^{123}I]MIBG was positive in 20 patients.

After these investigations, the patients were staged c.q. classified according to the Evans staging system [9], the TNM classification [10] and the International Neuroblastoma Staging System (INSS) [11]. 24 patients were Evans stage IV, 9 were stage III. According to the INSS criteria 23 were stage 4, 9 were stage 3, one was stage 2A. Among the 9 stage 3 patients, there were 4 inoperable abdominal tumours, 3 large thoracic tumours, 2 with intraspinal extension over several corporal vertebrae and 2 pelvic tumours with antero-end posterosacral extension of the tumour. All had clinical symptoms of cord compression.

Response was evaluated after completing the MIBG-treatment, prior to surgery and directly after surgery. These investigations included sonography for tumour measurement, 24-h urine collection for catecholamine excretion, serum ferritin, LDH levels, MIBG-scans and bone marrow aspiration and trephine biopsies during surgery. Response was scored according to the INSS criteria [11]. [^{131}I]MIBG with a specific activity of 30–40 mCi/mg was used. 3.7–7.4 GBq (100–200 mCi) [^{131}I]MIBG, diluted in 100 ml 0.9% sodium chloride and mounted in a lead shielded infusion system was administered intravenously over 4 h at a 4–6 week interval. During the process from dilution of the thawed infusion concentrate until the termination of infusion, radiochemical stability was tested to determine the degradation rate of [^{131}I]MIBG during the infusion [12]. Patients were admitted to nuclear protected hospital isolation for 4–6 days per treatment, dependent on local legislation, and needed to use potassium iodide orally for 2 weeks, starting 1 day prior to treatment in order to protect the thyroid from free ^{131}I. Daily scintigrams were made to monitor the pharmacokinetics of the agent *in vivo* and to estimate the absorbed radiation dose to the tumour. The total number of MIBG treatments depended on the response of the tumour and the estimation of the surgeon whether a resection of more than 95% of the tumour was feasible. For treatment protocol, see Figure 1. Whenever young children needed to be isolated, one of the parents or another close relative could stay in an adjacent room during the isolation period and was asked to take care of the child. This person also had to take potassium iodide orally. Continuous monitoring of the external radiation dose to the parents was performed.

If not in complete remission (CR) after surgery, four courses of chemotherapy were given. Four agents were used, vincristine 1.5 mg/m^2 day 1 with ifosfamide 3000 mg/m^2 i.v. in 3 h, days 1 and 2, carboplatin 400 mg/m^2 i.v. in 6 h, day 3 and VM-26 150 mg/m^2 in 2 h, day 4. After four courses of ablative chemotherapy with carboplatin 800 mg/m^2 day -3 and melphalan 180 mg/m^2 day -1 were administered followed by autologous bone marrow re-infusion on day 0.

RESULTS

33 consecutive neuroblastoma patients were entered into the study. All had at least two courses of MIBG. In 12 patients, a third course was given. Four courses were given to 5 patients, five to 5 patients, six to 2 patients and seven to one patient. The response of the primary tumour measured just before surgery was complete (CR) in 1, and partial (PR) (more than 50% reduction) in 18. Stable disease (less than 50% reduction) was noted in 11 patients. Three patients had progressive disease. Bone marrow was completely clear of tumour in 4 of 13 patients with bone marrow involvement at diagnosis. Urinary excretion of VMA and HVA decreased to less than 50% of that at diagnosis in 16 of 24 patients.

21 patients underwent surgery following MIBG induction therapy, of which 17 had a tumour resection of more than 95%. In 4, the resection was between 75 and 95%. In 5 other patients, no additional surgery was performed because there was no need. 7 patients were not operated on because of progressive disease or only after additional chemotherapy. 3 are still on pre-operative treatment. After surgery, 12 of 33 patients achieved a CR. There was one treatment-related death due to vascular bleeding 5 days

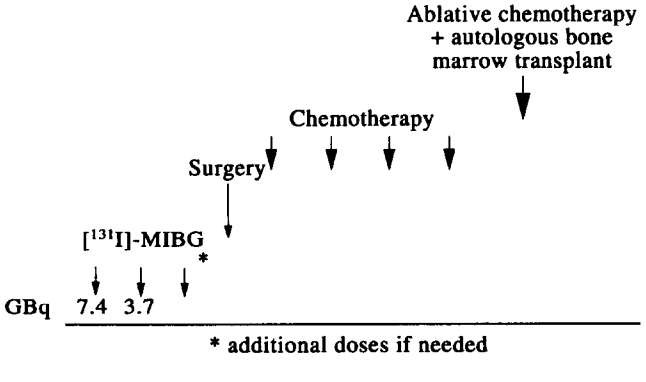

Figure 1. Treatment protocol for advanced stage neuroblastoma patients, as used in this series starting with [^{131}I]MIBG therapy. Chemotherapy = vincristine, etoposide, carboplatin, ifosfamide.

Table 1. The worst reported toxicity according to World Health Organisation criteria during the treatment with MIBG

	WHO Grading				
Toxicity*	0	1	2	3	4
Platelets	7	6	7	6	3
Transaminase	21	3	1	–	–
Creatinine	29	–	–	–	–
Alopecia	33	–	–	–	–
Vomiting	31	2	–	–	–
Weight loss	Mean 11% weight gain				

* Number of patients of worst reported toxicity.

after the surgical procedure. 16 patients are in continuous complete remission for 3–44 months from the date the complete remission was confirmed. 15 of these 16 are off treatment.

Toxicity of the MIBG Treatment

Haematological side-effects were observed, particularly thrombocytopenia (Table 1), but a decrease in neutrophils to less than 1000/ml was never observed. Blood transfusions were only necessary in 2 patients. Nephrotoxicity and hepatotoxicity were not observed in this population, and gastrointestinal toxicity above grade 1 was not seen. There were no side-effects directly related to the administration of the MIBG.

DISCUSSION

Even in advanced disease patients, it is feasible to obtain a remission rate of 70% or more with chemotherapy and surgery. However, the relapse rate is high among these patients, and many of them die because of drug resistance of the recurrent tumour. The idea of using radionuclide therapy as first line treatment is based on the hypothesis that targeted therapy is most effective in moderate to large tumour burden because of the "crossfire" effect from adjacent cells. Additional arguments are that no drug resistance is evoked and that this therapy leaves the general condition of the patient undisturbed. If effective in our study, a surgical resection of the primary tumour was performed, and in case of irradicality, chemotherapy of high intensity and short duration was instigated to achieve CR. The [^{131}I]MIBG therapy was given to all patients admitted to our hospital and who would have been treated by chemotherapy as first therapy modality in previous protocols.

The main interest of this study is to report on the feasibility of using [^{131}I]MIBG as pretreatment in patients with inoperable stage III tumours or patients with distinctive metastasis at diagnosis. The percentage of patients in CR or GPR after MIBG pretreatment and surgery was 69% which is similar to pre-operative chemotherapy and surgery [13].

After pre-operative MIBG treatment, three of the stage III patients did not have surgery because of normalisation of catecholamine excretion, serum ferritin, LDH and a shrinkage of the tumour to such an extent that the operation would have been unnecessarily mutilating, and a preventative approach was justified. These 3 children are in remission respectively for 3 years, 1 year and 10 months. The most striking effect of this type of treatment, however, was the pain relief within 24 to 48 h. Children with stage IV disease dying of pain, not able to walk, were happily walking around in the isolation room. Pain medication could be reduced to nil, their appetite recovered. Their pre-operative weight was 3–29% (mean 11%) greater compared to the pretreatment values with oral intake only. Thus, the palliative effect and quality of life improved dramatically. Patients not responding favourably to MIBG treatment did not deteriorate during this phase, and it was possible to switch to chemotherapy while they were still in the same or even better condition than at diagnosis. In 2 patients, the response to the MIBG treatment was so good, that surgery was not performed at all and no other adjuvant therapy was given. The tumour markers returned to normal, and radical surgery was considered to be too mutilating. Both children are alive without progression for 24 and 19 months, respectively.

Although the acute toxicity was extremely mild in comparison to intensive chemotherapy, it is not yet known what late effects can be expected. Studies are underway to investigate whether MIBG hampers the recovery of bone marrow after intensive chemotherapy or autologous bone marrow re-infusion. What we know so far from patients treated with ^{131}I for thyroid diseases is that the radionuclide treatment as well as the isolation are well tolerated. Major series in which patients were treated accordingly have been followed up for decades and show that side-effects and long-term complications of this treatment do not constitute a real problem. It is concluded that [^{131}I]MIBG treatment, as first line therapy, in advanced disease patients is feasible. Its effectiveness for attaining operability is at least equal to chemotherapy. Its side-effects, however, are considerably less. At this stage, it is too early to evaluate the outcome in terms of disease-free survival and overall survival.

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