Combined use of chemotherapy and ^{131}I-metaiodobenzylguanidine in the treatment of advanced-stage neuroblastoma

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Despite intensive chemotherapy, surgery and/or radiation, prognosis continues to be very poor in disseminated neroblastoma. Owing to neuroblastoma sensitivity progress might be achieved with high-dose radiation. Metaiodobenzyl guanidine (MIBG) coupled with ^{131}I provides the opportunity for highly selective radiation treatment of neuroblastoma, which could potentially deliver five to 10 times the dose of conventional external-beam treatment without specific tissue toxicity. To improve the long-term results in advanced-stage neuroblastoma, we integrated this new treatment modality with conventional chemotherapy. Eight neuroblastoma patients refractory to conventional treatment were treated with ^{131}I-MIBG-chemotherapy (vincristine, VP16, iphosphamide, carboplatin, epirubicin, cyclophosphamide) combination. Five of the eight patients responded to ^{131}I-MIBG treatment (2 complete and 3 partial responses). There were also three patients with stable disease. Median survival was 48 months (range 1 to 84 months), and five patients relapsed in their follow-up and died of progressive disease. We concluded that a combined ^{131}I-MIBG and chemotherapy approach is useful in advanced-stage neuroblastoma patients, with considerably less side effects. Although survival is improved when compared to conventional treatment, the overall prognosis is still poor. More lethal radionuclide conjugation to MIBG which will deliver higher tumor and lower critical organ doses may offer the best solution for targeted radionuclide therapy of neuroblastoma.

Key words: ^{131}I-metaiodobenzylguanidine (MIBG), neuroblastoma, radionuclide therapy.

Despite intensive chemotherapy, surgery and/or radiation, prognosis continues to be very poor in disseminated neuroblastoma[1]. Even with myeloablative megatherapy regimens combined with stem-cell transplantation, the five-year survival for children with metastatic neuroblastoma is less than 20 percent[2,3]. Owing to neuroblastoma sensitivity, progress might be achieved with high-dose radiation. However, delivery of high-dose radiation is limited by host tolerance. This has led to a search for new treatment approaches that will not increase toxicity to normal tissues but will allow greater antitumor efficacy[4]. Metaiodobenzylguanidine (MIBG) is a guanethidine derivative with a structure analogous to norepinephrine which permits selective concentration in sympathetic nervous tissue[5]. MIBG coupled with ^{131}I provides the opportunity for highly selective radiation treatment of neuroblastoma[6]. The most important feature of this approach is the ability to specifically target the tumor tissue while limiting or minimizing the radiation dose to most normal organs, which could potentially deliver five to 10 times the dose of conventional external-beam treatment without specific tissue toxicity[7]. Although complete and partial responses have been reported in patients resistant to conventional therapy with ^{131}I-MIBG as a first-line treatment at diagnosis, long-term results are still unsatisfactory[8,9]. Inhibition of repair of potentially lethal radiation damage and a synergistic action are possible with the combined use of chemotherapeutics and ^{131}I-MIBG[10].

To impprove the long-term results in advanced-stage neuroblastoma, we integrated this new treatment modality with conventional chemotherapy.

Material and Methods

Patients

Eight patients (6 girls, 2 boys) with histologically proven neuroblastoma refractory to conventional treatment and whose tumors had concentrated ^{131}I-MIBG on diagnostic imaging were entered into the study between 1995-1999. Ages ranged from four to 12 years, and a life expectancy of at least four weeks as required to enter the study. Patients were staged occording to the Evans staging system[11]. Four were stage IV and four were stage III at the time of diagnosis. Five patients had right adrenal lesion, one had left adrenal lesion, one had presacral and orbital lesion and one had left adrenal, bone and bone marrow involvement.

Treatment with ^{131}I-MIBG

Patients were prepared for the ^{131}I-MIBG with thyroid blocking agent potassium iodide (lugol's solution) starting three days prior to treatment for two weeks to prevent uptake of radioactive iodine by the thyroid gland. Drugs known or expected to reduce MIBG uptake were discontinued one week prior to treatment. ^{131}I-MIBG shipped in dry ice was thawed and diluted in 200 ml 0.9% sodium chloride according to the manufacturer's instructions (Amersham, UK) and administered intravenously via a lead shielded system over two hours. Appropriate radiation safety measures were taken, and patients stayed in hospital isolation until the exposure measure 1 meter from the patient's surface was less then 4 mR/hour. A total of 15 ^{131}I-MIBG therapies were given. The administered activity ranged between 100-200 mCi per treatment, and the radiounclide therapy was repeated at a minimum of four to six week intervals with a maximum cumulative activity of 450 mCi (range: 100-450 mCi).

Chemotherapy Regimens

Two different types of combined chemotherapy regimens were used before ^{131}I-MIBG therapy. Two patients were treated with the classic NBL protocol consisting of vincristine (1.4 mg/m^2), cyclophosphamide (800 ng/m^2), and cisplatin (90 mg/m^2), weekly for three weeks.

Bristol II chemotherapy regimen consisting of vincristine (1.4 mg/m^2), VP-16 (100 mg/m^2 over 3 days), carboplatin (250 mg/m^2), and epirubicin (50 mg/m^2) was administered to three patients at four-week intervals.

Definition of Response Status

Investigations for response evaluations included computed tomography and/or ultrasound, diagnostic MIBG scans, ^{99}mTc-MDP bone scans, bone marrow aspiration and measurement of urinary catecholamine metabolites. International Neuroblastoma Response Criteria were used to describe response[13]. Complete remission corresponds to complete disappearance of all measurable tumor. Partial remission describes a greater than 50 percent disease reduction in primary and metastatic sites. Stable disease and minor response refer to any response of less than 50 percent. Progressive disease indicates progression at any preexisting tumor site or appearance of a new leison.

Results

Patient characteristics and response to treatment are listed in Table I.

Table I. Patient Characteristics and Response to Treatment

Patient no.	Sex/age (years)	Tumor localization at diagnosis	Stage at diagnosis	Chemotherapy protocol	Cumulative MIBG dose and number of treatments	Outcome	Response to treatment	Survival (months)
1. ZY	M/5	Left adrenal	III	Bristol	150 (1)	Exitus	PR	48
2. ANÇ	F/4	Presacral, orbital	IV	Classic NBL	225 (2)	Exitus	CR	18
3. CB	F/2	Right adrenal	III	Classic NBL	275 (2)	Exitus	SD	12
4. FA	F/4	Right adrenal	III	Classic NBL	100 (1)	Exitus	CR	23
5. TG	F/5	Bone, bone marrow, left adrenal	IV	Bristol	200 (1)	N/A	SD	1
6. SÖ	F/10	Right adrenal	III	Bristol	400 (3)	Exitus	PR	84
7. EGD	F/5	Right adrenal	IV	Classic NBL+Bristol	450 (2)	Alive	PR	40
8. AÖ	M/14	Right adrenal	IV	Classic NBL+Bristol	450 (3)	Alive	SD	31

CR: complete; PR: partial remission; SD: stable disase; MIBG: metaiodobenzylguanidine; N/A: not available (lost to follow-up).

Toxicity of the ^{131}I-MIBG Treatment

Most patients reported mild nausea on the first day. Mild to moderate hematopoietic toxicity occurred in three patients, with a decrease in platelet and white blood cell counts. One patient developed hypothyroidism diagnosed by elevated thyroid-stimulating hormone and low thyroxine levels.

Response and Survival

Five of the eight patients responded to ^{131}I-MIBG treatment (2 complete and 3 partial responses). In two patients, response was achieved after one course of treatment, and in three patients response was achieved after more than one course. There were also three patients with stable disease. This disease stabilization occurred in patients with actively progressing disease at the time of treatment.

Survival is shown in Figure 1. The median survival was 48 months with Kaplan-Meier analysis (range 1 to 84 months). Five patients relapsed in their follow-up and died of progressive disease (Fig. 2). One patient's survival was unknown as he did not admit to haspital again. Two patients are still alive, one with progressive disease and one with stable disease; both received more than one course of treatment and a total cumulative dose of 450 mCi (Fig. 3).

Discussion

Outcome of advanced-stage neuroblastoma patients is still poor despite intensified chemotherapy regimens and bone marrow rescue. Stage III and IV neuroblastoma patients have two-year survival rates of only 30 and 10 percent,

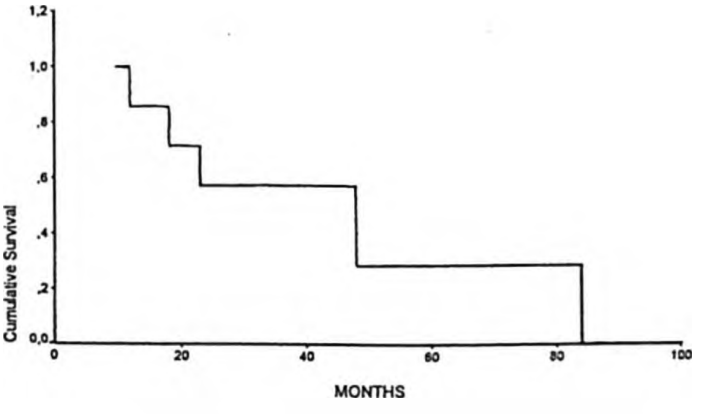

Fig. 1. Survival of patients treated with ^{131}I-MIBG-chemotherapy combination.

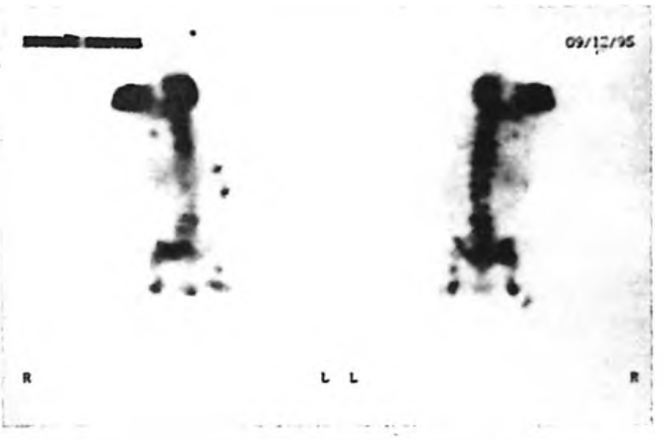

Fig. 2. Post-therapy ^{131}I-MIBG scan of patient (no. 6) treated with a cumulative dose of 400 mCi of ^{131}I-MIBG. Patient had a very good response to initial therapy but died of progresive disease at the end of 84 months.

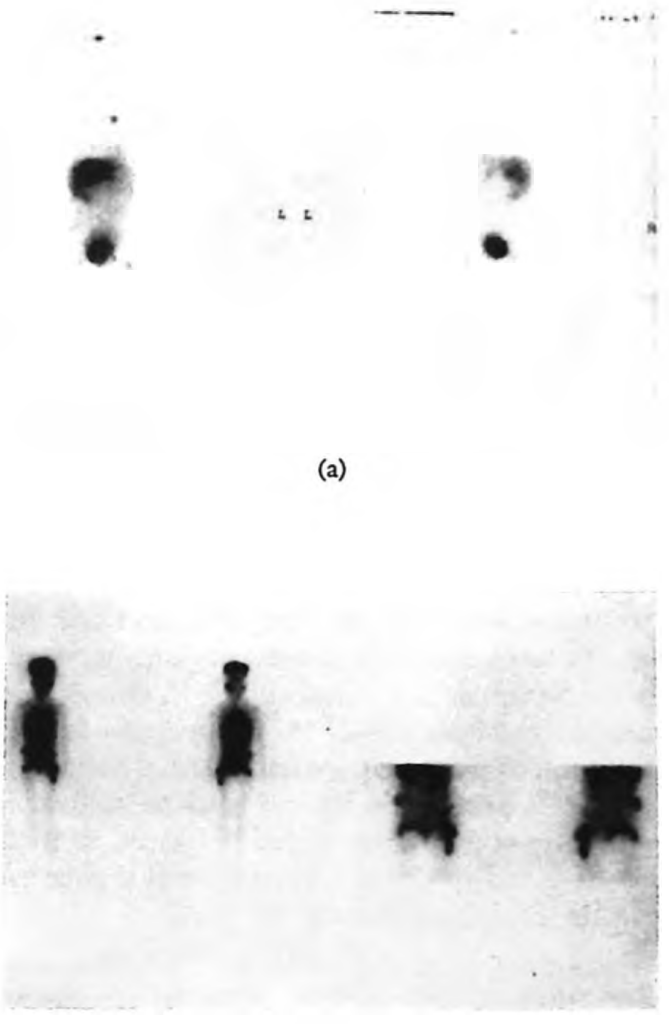

Fig. 3: Whole body scintigraphies of patient no. 7 after 1st (a) and 3rd (b) course of ^{131}I-MIBG treatment. After a good partial remission patient showed a progressive trend and widespread metastasis occurred, including brain metastases.

respectively[12]. The relapse rate is high among these patients and many of them die because of drug resistance of the recurrent tumor.

In this study we treated eight patients using a combination of ^{131}I-MIBG and chemotherapeutics which resulted in a median survival of 48 months at the end of a four-year follow-up. Two children with severe pain due to bone metastases who were unable to walk began walking and their pain medication was decreased. The acute toxicity was mild in comparison to that with intensive chemotherapy. Although the combined treatment approach increased survival and life quality of these patients,, overall prognosis was still poor. Five of our patients died due to recurrent disease and one of them developed progressive disease after a good response to initial ^{131}I-MIBG treatment. However, the patients studied here were heavily pretreated, with highly resistant disease. Moreover, the very extensive prior treatment may have increased the severity of the hematological toxicity. We believe ^{131}I-MIBG combined with chemotherapy should be attempted at an earlier stage of the disease, with the possibility of even better results and less hematological toxicity. De Kraker et al.[9] treated 33 previously untreated advanced-stage neuroblastoma patients with ^{131}I-MIBG and concluded that ^{131}I-MIBG as a first-line therapy is at least equal to chemotherapy, with less side effects. The integration of this new treatment modality with chemotherapy as a first-line therapy may give better results. However, dose schedule studies are required to establish toxicity and efficacy[14].

Preclinical trials in cultured cells and animal tumors have established a synergism between chemotherapeutics and radiation[15,16]. One of the possible mechanisms of this synergism is the inhibition of repair of potentially lethal radiation damage[17]. Better results can also be achieved by the use of no-carrier-added ^{131}I-MIBG so that the predicted tumor absorbed dose is higher by a factor of approximately 2.3[18].

We conclude that a combined ^{131}I-MIBG and chemotherapy approach is useful in advanced-stage neuroblastoma patients with considerably less side effects. Although survival is significanly improved compared to conventional treatment, the overall prognosis is still poor. More lethal radionuclide conjugation to MIBG which will deliver higher tumor and lower critical organ doses may offer the best solution for targeted radionuclide therapy of neuroblastoma[19].

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