Original Article

Management of neuroblastoma. Comparative study between first- and second-line radioionated meta-iodobenzylguanidine therapy and chemotherapy alone

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ABSTRACT

Context: Neuroblastoma is a high-grade malignancy of childhood; it is chemo- and radio-sensitive, but prone to relapse after initial remission. **Aim:** The aim of this study was to document the impact of first- or second-line radioionated [^{131}I] meta-iodobenzylguanidine (^{131}I-MIBG) therapy or chemotherapy alone on the short-term response and long-term survival in untreated children and to further characterize the side-effects of MIBG treatment. **Materials and Methods:** In this interventional randomized controlled study, 123 children with advanced neuroblastoma were divided into three groups according to the treatment strategy: 65 were treated by chemotherapy alone (group I), 30 children who were not responding or had relapsed after chemotherapy were treated by second-line ^{131}I-MIBG (group II), and 28 children were treated by ^{131}I-MIBG as first-line from the start (group III). External beam radiotherapy was given to bone and brain secondaries when detected. Staging work up was done before, during, and after management with a follow-up period of 5 years. **Statistical Analysis Used:** All statistical tests were done using Whitney test for the continuous variants to compare the same group pre- and post-therapy. Total actuarial survival and disease-free survival were calculated using Kaplan–Meier analysis. **Results:** The number of treatments with ^{131}I-MIBG varied between 1 and 4 per patient (mean 3). Toxicity was seldom severe. Mainly myelosuppression was noticed. Response was documented before surgery for the primary tumor was performed. There was 9, 6, and 14 complete response (CR); 10, 18, and 16 partial responses (PR); 3, 2, and 23 with a stable disease (SD); and 6, 4, and 12 progressed in each group, respectively. Total actuarial survival was found to have a median of nearly 60, 55, and 33 months for groups I, II, and III, respectively, with a statistical significant difference between the three groups. **Conclusion:** The current study showed the effectiveness of MIBG as a first-line treatment in the management of locally advanced neuroblastoma cases with limited metastasis as initial response and long-term survival for the cases was favorable, while in cases with multiple metastases, chemotherapy should be given first-line and, in case of failure or relapse, second-line MIBG therapy is warranted.

Key words: [^{131}I] meta-iodobenzylguanidine, neuroblastoma, targeted therapy, chemosensitive, radiosensitive

INTRODUCTION

Neuroblastoma, the most common extra-cranial solid tumor of childhood, has a long-term survival rate of only 15%.[1] At diagnosis, the defining characteristics of high-risk neuroblastoma include an age of >1 year, metastases, amplification of the *N-MYC* oncogene, and histological findings.[2-4] Recent progress in the treatment of high-risk neuroblastoma may be due to the use of higher doses of chemotherapy[5] and improved supportive care.

Treatment of advanced neuroblastoma remains unsatisfactory. The standard treatment of combination chemotherapy followed by surgery induces a complete remission in about 40% of cases; however, more than half subsequently relapse and the long-term survival rates at best are <20%. In an attempt to improve results in this group of patients, intensive treatment protocols, referred to as "mega therapy," which combine high dose chemotherapy and/or

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total body irradiation (TBI) with autologous bone marrow transplantation (BMT) have been developed.[1,4,6]

Targeted radionuclide therapy with [^{131}I] meta -iodobenzylguanidine (^{131}I-MIBG), a catecholamine analog selectively taken up by cells of neural crest origin, was first used for the treatment of neuroblastoma after discovering that, similar to 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 using this treatment modality.[7] Due to the palliative ability of ^{131}I-MIBG treatment as well as its positive impact on response and survival rates in advanced and refractory cases,[8,9] authors were encouraged to evaluate its therapeutic value regarding early cases.

Although the exact mechanism of uptake of ^{131}I-MIBG remains unclear, it is believed to have the same uptake and storage mechanism as that of nor-epinephrine in two ways: First, a sodium-dependent system with a high affinity but low capacity, which is easily saturated, and, second, a sodium-independent, apparently unsaturatable process of passive diffusion.[6] Unlike nor-epinephrine, MIBG is not metabolized and is excreted unaltered via the kidneys; 70-90% of the administered activity is recovered in the urine within 4 days.[10]

It has become clear, however, that the most prominent responses were obtained in patients with a large tumor burden at the time of treatment. This finding has served as the basis for ^{131}I-MIBG therapy whether first- or second-line.[5]

The primary endpoint of the current study was to document the impact of first-or second-line MIBG therapy or chemotherapy alone on the short-term response and long-term survival in untreated children and to further characterize the side-effects of MIIBG treatment.

MATERIALS AND METHODS

Between June 2007 and August 2011, 123 neuroblastoma patients diagnosed at the Paediatric Oncology Unit of Alhada Military Hospital, Taif, Saudi Arabia were included in the present study with a minimal follow-up of 2 years. The institutional review boards (in both Faculty of Medicine, Taif University and Al Hada Military hospital) approved our study and was made aware of the additional radiation dose. A written informed consent was obtained from all parents of sick children before initiation of the treatment. They were either children with Evans stages III and IV, who were newly diagnosed to be treated randomly with either chemotherapy alone (group I) or first-line MIBG therapy (group III), or those who failed after initial successful therapeutic modalities (group II). MIBG was given, as either second- or first-line therapy, to patients aged <16 years with performance status >30% (K.I.). Additional inclusion criteria for ^{131}I-MIBG therapy were a reasonable selective uptake and retention of ^{131}I-MIBG in diagnostic MIBG imaging, platelets >50,000/mm^3, serum creatinine <1.5 mg/dl, and a written consent.

Accordingly, children included in the chemotherapy group alone were 65, and all were treated by 6 cycles of alternating courses of OPEC/OJEC—vincristine 1.5 mg/m^2 (O), cisplatin 80 mg/m^2 (P), etoposide 200 mg/m^2 (E), cyclophosphamide 600 mg/m^2 (C), and carboplatin 500 mg/m^2 (J)—every 21 days, if there was hematological recovery. Second-line ^{131}I-MIBG therapy was given to 30 children. The age ranged from 1 year to 15 years, with a median age of 5 years. All children were subjected to the same chemotherapy (C/T) for 6 cycles, followed by MIBG scanning when no response or residual tumor was observed following C/T.

First-line ^{131}I-MIBG therapy was given to 28 children from the start on an investigational basis.

External beam radiotherapy was given to bone and brain secondaries when detected, irrespective of the group.

Diagnostic work up

- A full clinical examination with documentation of all measurable diseases
- Performance status using K.I and body weight in kilogram
- Laboratory investigations: CBC including platelets, BUN, serum creatinine, LDH, ESR, and urinary vanillylmandelic acid (VMA).
- Bone marrow aspiration and tumor biopsy
- Radiological imaging: Chest X-ray, CT scan of the tumor site, and abdomino-pelvic sonography
- Radionuclide imaging: Bone scan and ^{131}I-MIBG scans

VMA was elevated in 27/30 patients in group II (90%) with a median of 250 μg/mgm of creatinine and in all children of group III. Figure 1 shows the number of courses of ^{131}I-MIBG given to patients in the present study either as a first-or second-line.

To prevent uptake of ^{131}I by the child's thyroid, an oral dose of 100 mg potassium iodide was administered daily, starting 1 week before and for 1 week after ^{131}I-M1BG therapy. A fixed dose of 100 mci ^{131}I-MIBG was administered over a 4-h infusion using a lead-shielded infusion pump. This dose was repeated every 4 weeks for 2-3 courses.

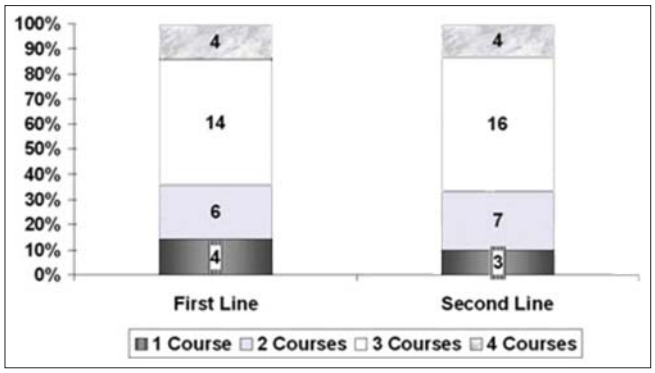

Figure 1: Distribution of patients of meta-iodobenzylguanidine groups according to the number of courses of MIBG therapy

Patients were isolated in a private room for 4-6 days and were injected with dexamethasone at a dose of 8 mg/m^2, then prednisone 60 mg/m^2 orally for 7 days to guard against laryngeal oedema and other radiation effects. Parents were instructed to participate in their children's care thereafter. On the 5th day post-MIBG therapy, whole-body scintigraphy, both anteriorly and posteriorly, was done for all patients. Assessment of response was done pre- and post-therapy at the end of all courses by ^{131}I-MIBG scintigraphy, bone scan, CT scan of the primary tumor, bone marrow aspiration, and VMA level estimation.

Criteria of response of 13/f MIBG therapy were as follows:[8]

- Complete response (CR): >90% decrease in tumor volume
- Partial response (PR): 50-90% decrease in tumor volume
- Stationary disease (SD): <50% decrease in tumor volume
- No response (NR): No change in the size of the tumor
- Disease progression (DP): Increase in the size of the tumor

Statistical methods

The prevalence of the observed results was calculated in the studied group pre- and post-therapy using normal proportion methods (observed results/total number of the groups). The continuous variants were compared for the same group pre- and post-therapy using Whitney test. For calculation of the (total actuarial survival, and disease-free survival) (TAS and DFS) indices, Kaplan–Meyer's method was used.

RESULTS

Patient characteristics are summarized in Table 1, as follows in brief:

Primary tumors were found in the thorax in 7 cases (25%) in group III, 7 (23.3%) in group II, and 18 (27.7%) in group I. On the other hand, primary abdominal tumors were found in 21 cases (75%) in group III, 25 (83.3%) in group II, and 47 (72.3%) in group I.

Table 1: Distribution of children according to site of the tumors and staging

	First-line MIBG		Second-line		Chemotherapy Alone	
	No.	%	No.	%	No.	%
Primary tumor						
Thoracic	7	25	7	23.3	18	27.7
Abdominal	21	75	25	83.3	47	72.3
Metastases						
Lymph nodes	16	57	15	50	30	46.2
Bone marrow	9	32	15	50	39	60
CNS	2	7.1	7	23.3	1	1.5
Bone	7	25	11	36.7	38	58.5
Soft tissue	1	3.6	4	13.3	2	3.1
Evan stage						
III	11	39.3	6	20	15	23.1
IV	17	60.7	24	80	50	76.9

CNS: Central nervous system

Concerning metastasis, lymph node metastases were present in 16 (57%), 15 (50%), and 30 cases (46.2%) in groups III, II, and I, respectively. Bone marrow (BM) was positive in 9 (32%), 15 (50%), and 39 cases (60%), respectively. CNS metastases prevailed in 2 (7.1%), 7 (23.3%), and 1 case (1.5%), respectively, in the three groups. Bone secondaries were diagnosed in 7 (25%), 11 (36.7%), and 38 cases (58.5%), respectively, in the three groups. Soft tissue metastases were detected in 1 (3.6%), 4 (13.3%), and 2 cases (3.1%) in the three groups, respectively.

Staging

Evan stage III cases were 11 (39.3%), 6 (20%), and 15 (23.1%) and Evan stage IV cases were 17 (60.7%), 24 (80%), and 50 (76.9%) in first- and second-line ^{131}I-MIBG treated groups and chemotherapy group, respectively.

General conditions

Both performance status [Figure 2] and body weight [Figure 3] improved significantly after MIBG therapy, the average K.I. was 65.7, 68.9, and 66.2% pre-therapy and increased significantly to 89.7, 82.4, and 84.9% post-therapy in the first-line, second-line ^{131}I-MIBG treated groups, and chemotherapy group, respectively. The increase in the body weight in the three groups was to a statistically significant extent, with the least increase seen in the chemotherapy group.

Short-term assessment (Response)

Response in the primary tumors

The response rates of patients in the primary tumor site were as follows [Table 2]: CR was achieved in 9/28 (32.1%), 6/30 (20%), and 14/65 (21.5%) in the first-line, second-line I^{131}-MIBG treated groups, and chemotherapy group, respectively. PR were observed in 10 (34%), 18 (60%), and 16 cases (24.6%) in the three groups, respectively. SD in 3 (10.7%), 2 (6.7%), and 23 cases (35.4%) in the three

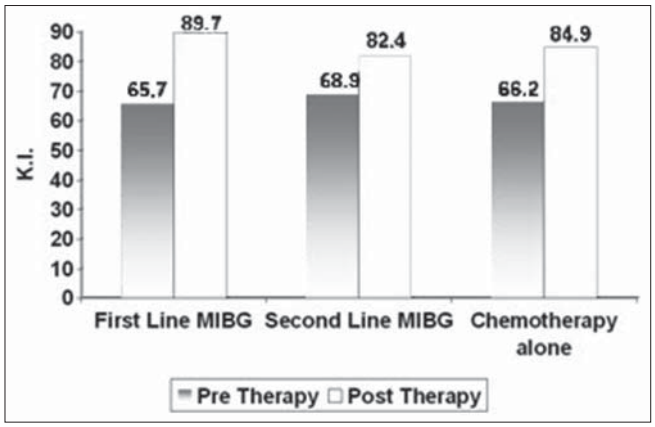

Figure 2: Comparison between the mean values of Karnofsky scale pre and post treatment

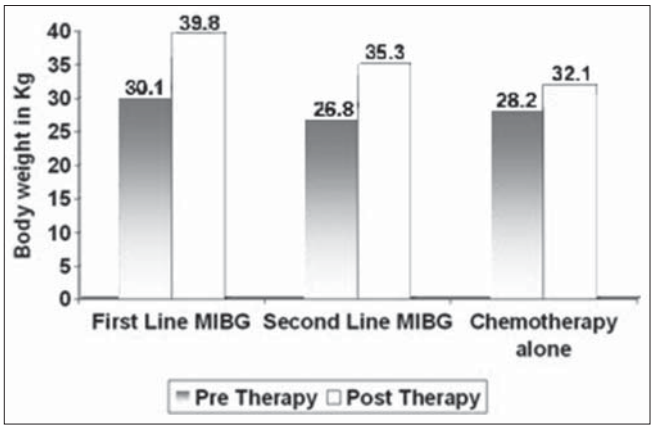

Figure 3: Comparison between the mean values of body weight pre and post treatment

Table 2: Response rate in primary tumor sites in the studied groups

Degree of response	First-line MIBG		P1	Second-line MIBG		P2	Chemotherapy		P3
	No.	%		No.	%		No.	%	
CR	9	32.1	<0.05	6	20	>0.05	14	21.5	<0.05
PR	10	34	<0.01	18	60	<0.01	16	24.6	>0.05
SD	3	10.7	>0.05	2	6.7	<0.01	23	35.4	<0.01
NR	1	3.6	>0.05	1	3.3	>0.05	5	7.7	>0.05
DP	5	17.9	>0.05	3	10	>0.05	7	10.8	>0.05

P1: Comparison between first- and second-line MIBG, P2: Comparison between second-line MIBG and chemotherapy, and P3: Comparison between chemotherapy and first-line meta-iodobenzylguanidine, CR: Complete response, PR: Partial responses, SD: Stable disease, NR: No response, DP: Disease progression

groups, respectively. No response was observed in 1 (3.6%), 1 (3.3%), and 5 cases (7.7%) in the three groups, respectively. Disease progression was observed in 5 (17.9%), 3 (10%), and 7 cases (10.8%) in the three groups, respectively. Collectively, responses in the form of CR and PR in the primary tumor sites were statistically higher in the MIBG therapy groups whether first- (66.1%) or second-line ^{131}I-MIBG treated groups (80%) versus the chemotherapy treated group (46.1%) ($P < 0.05$).

Regarding the impact of metastasis on the response [Table 3], it was found that none of those 9 cases with CR in the first-line ^{131}I-MIBG had metastasis, while 2/6 (33.3%) with CR in the second-line, and 3/14 (21.4%) in the chemotherapy group had metastasis. In those achieving PR, 2/10 (20%), 16/18 (88.9%), and 9/16 (56.3%) in the first-line, second-line ^{131}I-MIBG, and chemotherapy groups, respectively, had metastasis. On the other hand, 1/3 (33.3%), 2/2 (100%), and 20/23 (86.9%) in the three groups, respectively, with SD had metastasis. Concerning non-responders in the form of NR or DP, all cases in the three groups who were non-responders had metastases.

Long-term assessment (Survival)

Figure 4 revealed the total actuarial 5-year survival of the studied groups during the follow-up period. The median survival was found to be statistically highest in the first-line MIBG therapy group, which could not be reached with the end of the follow-up period and approached in the current study nearly 60 months. Whereas, it was 51 months for the chemotherapy group with $P < 0.05$ on comparing survival between the two groups and it was lowest in the second-line ^{131}I-MIBG group (33 months) with $P < 0.01$ on comparing survival between this group and the other two groups.

On the other hand, at the end of the follow-up period (5 years), it was found that 55% of the first-line group, 40% of the chemotherapy group, and 14% of the second-line group were still alive.

Toxicity

The first-line MIBG therapy group showed grade I myelosuppression in 5/28 cases (17.9%) and hemorrhage in 1 case. Whereas, the second-line MIBG therapy group showed grades I and II myelosuppression in 21/30 cases (70%), abdominal distension in 20/30 cases (66.7%), and severe hemorrhage in 1 case. The chemotherapy group showed grades II and III myelosuppression in 39/65 cases (60%), grades II andIII vomiting in all cases, and grade III alopecia in all cases.

DISCUSSION

The current study revealed that first-line ^{131}I-MIBG therapy

Table 3: Impact of the presence of metastases on the response rate in the studied groups (initially metastatic)

Degree of response	First-line MIBG		P1	Second-line MIBG		P2	Chemotherapy		P3
	No.	%		No.	%		No.	%	
CR	0/9	0	<0.05	2/6	33.3	>0.05	3/14	21.4	<0.05
PR	2/10	20	<0.01	16/18	88.9	<0.05	9/16	56.3	>0.05
SD	1/3	33.3	<0.05	2/2	100	>0.05	20/23	86.9	<0.01
NR	1/1	100	>0.05	1/1	100	>0.05	5/5	100	>0.05
DP	5/5	100	>0.05	3/3	100	>0.05	7/7	100	>0.05

P1: Comparison between first- and second-line MIBG, P2: Comparison between second-line MIBG and chemotherapy, and P3: Comparison between chemotherapy and first-line meta-iodobenzylguanidine, CR: Complete response, PR: Partial responses, SD: Stable disease, NR: No response, DP: Disease progression

was the most effective regarding short-and long-term control of locally advanced tumors. The highest CR and longest median survival (approximately 60 months) was observed in this group, but it was least effective with multiple metastases. On the other hand, second-line ^{131}I-MIBG therapy was found to be effective in controlling patients with multiple distant metastases with highest percentage of PR, but worst regarding survival with a median survival of 31 months. Concerning chemotherapy alone, it was found to be effective in inhibition of tumor spread. This arm also had the highest incidence of SD with a midway median survival of 51 months.

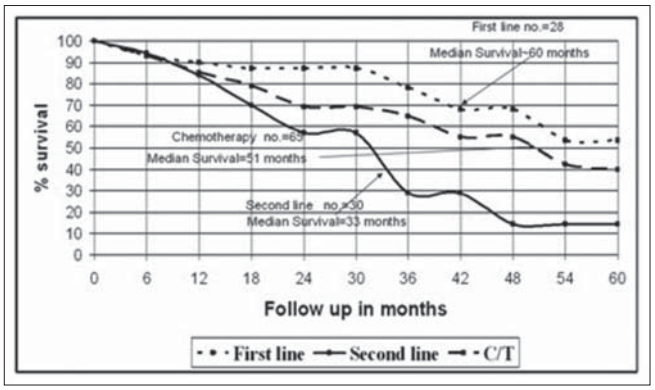

Figure 4: Comparison between total actuarial survival of the studied groups

Advanced neuroblastoma and conventional management

Even in cases with advanced disease, it is possible to obtain a remission rate of 70% or more with chemotherapy and surgery.[11] However, the relapse rate is high among these patients, and many of them die because of the refractory recurrent tumor.[2,3,5] In the current study, the majority of the chemotherapy alone treated patients (group I) showed SD (35.4%) rather than CR (21.5%) or PR (24.6%), and the addition of second-line ^{131}I-MIBG (group II) enhanced the response in such a way that it increased the incidence of PR to be 60% and reduced the incidence of SD.

Concerning survival, in the Spanish neuroblastoma group, the probability of survival with stage IV disease was 0.24 at 5 years.[12] Moreover, Philip, *et al*.[13] reported an outcome of 32% survival at 5 years for patients given a highly intensive investigational megatherapy. The toxicity death rate in this group of 33 patients was 24%. In the European registry, overall survival after 5 years was not more than 33% for stage 3 and stage 4 patients.[14] The current study revealed a 40% survival in the chemotherapy group (group I), which is very similar to the Euproean study[14] and Philip, *et al*.[13] and higher than that of the Spanish group.[12] However, in the current study, this value of survival was decreased markedly to 14.1% at 5 years in the second-line MIBG group (group II) due to increased toxicity mainly in the form of severe myelosuppression. Moreover, those children were mostly metastatic with a poor performance status reducing the tolerance for both chemotherapy and ^{131}I-MIBG.[7,10] On the other hand, when MIBG was used alone (group III) as first-line, survival was highest at 5 years (55%) that is attributed to the salvage surgery performed following neo-adjuvant radionuclide therapy, which represents 66.1% of the children of this group.

Advanced neuroblastoma and targeted radionuclide therapy

^{131}I-MIBG therapy has been used since the 80s in Europe and the United States as a single palliative agent for chemo-refractory cases or more recently in combination with myeloablative therapy before bone marrow rescue. Other applications of ^{131}I-MIBG therapy have been unresectable stage 3 disease, first-line therapy in combination with chemotherapy, and consolidation therapy after induction of a major partial remission.[5]

Sixty percent of neuroblastomas in young children reported by the literature are stage 4 (undifferentiated and widely disseminated) at diagnosis, which is very close to the percentage reported in the current study, where 91/123 (73.9%) were Evan's stage IV.[6,12] In these cases, new treatment strategies are needed as the results of the conventional treatment modalities are not satisfactory. Inclusion of ^{131}I-MIBG therapy is highly desirable because of the high specificity of the agent and the radio-sensitivity of the primary and metastatic tumors.

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 tumor burden patients because of the "crossfire" effect from adjacent

cells.[15] Additional arguments are that no drug resistance is evoked and that this therapy leaves the general condition of the patient undisturbed,[1,15] very similar to the current study findings that revealed a significant improvement in the general condition in the form of performance status and body weight. If ^{131}I-MIBG is effective in the current study, a surgical resection of the primary tumor should be performed, and in case of incomplete surgery, chemotherapy of high intensity and short duration was given to achieve CR. The ^{131}I-MIBG therapy was given randomly to children admitted to our hospital and who would have been treated by chemotherapy as a first-line therapy modality after obtaining a written consent from the parents. The main interest of this study is to report on the feasibility of using ^{131}I-MIBG as a neo-adjuvant treatment in patients with inoperable stage III tumors or patients with distinctive metastasis at diagnosis. The percentage of patients in CR or PR after MIBG pretreatment and surgery was 66.1% and 80%, respectively, for first- and second-line ^{131}I-MIBG therapy, which is similar to preoperative chemotherapy and surgery percentages reported previously.[15,16]

One of the most important explanations for the impressing response of neuroblastoma to MIBG therapy was reported by Voute, *et al*.[17] who stated that in addition to the radiation effect produced by the locally trapped radioactive ^{131}I, MIBG in itself is an inhibitor of complex I, which is part of the enzyme system situated in the mitochondrial respiratory chain. Inhibition of complex I leads to the leak of paired electrons out of the respiratory chain, which causes an increased production of the superoxide radical. This superoxide radical is normally converted into hydrogen peroxide by the enzyme superoxide dismutase, subsequently, the hydrogen peroxide is converted into harmless water and oxygen in a reaction catalyzed by catalase. However, when catalase activity is reduced, as in neuroblastoma cells, the hydrogen peroxide will partly be converted into the very reactive oxygen-derived free radical, the hydroxyl radical, which contributes to further elevation in the contents of the free radicals mainly the superoxide and hydroxyl radicals. Utilizing MIBG for neuroblastoma treatment, therefore, adds a fourth factor in damaging the tumor cells, whereas the radioactivity of ^{131}I-MIBG can be considered a fifth contributing factor.

Toxicity

In ^{131}I-MIBG therapy, the bone marrow is the dose-limiting organ.[18] In a cohort of patients with neuroblastoma who had received prior intensive chemotherapy, it has been shown that the dose-limiting toxicity of a single-fraction of ^{131}I-MIBG is myelotoxicity at a 2.5 Gy whole-body dose.[10,18] This is very similar to current study that revealed myelosuppression in 17.9% of the cases in first-line MIBG therapy, but it increased to 70% in second-line MIBG therapy due to the additive effect of previous chemotherapy toxicity. Matthay, *et al*.[7] considered a total dose of 4.0 Gy (whole-body dose), followed by stem-cell rescue is well-tolerated with no other short-term organ dose-limiting toxicity.

As a dose–toxicity relationship was previously established between bone marrow suppression and the whole-body dose, which can be used as a surrogate for marrow dose, pre-therapy dosimetry ^{123}I-mIBG scanning can be used to predict the individual degree of bone marrow toxicity.[8] That is why two major lines of ^{131}I-MIBG treatment developments are taking place. Both involve ^{131}I-MIBG dose escalation to increase the tumoral radiation dose further, but differ in methodology. In the United States, the "San Francisco approach" gives a high activity of ^{131}I-MIBG (15–18 mCi/kg, about 550-660 GBq/kg) with stem cell support available. This activity amount was previously established from toxicity–dose relationship phase I studies.[9] Whole-body (and tumor) dose are calculated after therapy and a second treatment is administered if necessary, based on the correlation of radiation dose and observed toxicity.[19] The advantage is that there is no need for more or less accurate planning/simulation. The disadvantages are the wide range of whole body (and tumor) doses that will still exist, and the risk of individual under- or overtreatment and unpredictable myelotoxicity to the patients. Howard, *et al.* reported the feasibility of repetitive ^{131}I-MIBG and achieved a 39% overall disease response in 24 heavily pretreated patients.[20]

The European "ESIOP ^{131}I-MIBG-protocol" is dedicated to patients with high-risk neuroblastoma who failed to achieve adequate partial remission after induction chemotherapy. It uses high activities of MIBG, combined with topotecan,[21] in order to deliver a total combined whole-body dose of 4.0 Gy in two fractions. A stem cell rescue is required after the second fraction. Relatively simple dosimetry is performed after the first fraction and calculates the activity to be administered in the second fraction. This allows a very homogeneous total activity dose to the patients and also allows better study of the relevant parameters, i.e., whole-body and tumor doses. The feasibility of this protocol was recently tested in a phase I study in 8 children.[22]

CONCLUSION

The current study concludes that locally advanced tumors with one or two distant metastases can be managed by first-line ^{131}I-MIBG therapy, while in children with multiple distant metastases, chemotherapy should be considered as a first-line therapy in such a way that at least it could stop the spread of metastasis, and those children who failed to respond to chemotherapy alone or relapsed could benefit

from the second-line ^{131}I-MIBG therapy with an increase in the risk of hematological toxicity.

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