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^{131}I MIBG as a Second Line Therapy in Children with Advanced Neuroblastoma

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ABSTRACT

Objectives: To evaluate the role of ^{131}I MIBG as a second line therapy in patients with advanced Neuroblastoma.

Patients and Methods: 30 children with advanced Neuroblastoma who were either refractory to conventional chemotherapy or showed disease relapse after initial succesful treatment, received ^{131}I MIBG as a second line therapy in a dose of 100 mci per course, at 4 weeks interval for 3-4 courses. Patients were isolated in private rooms, and given dexamethazone to guard against laryngeal oedema and other radiation effects. on the 5th day post MIBG therapy, whole body scintigraphy was done to all patients. Assessment of response was done at the end of therapy by CAT scan, bone scan, ^{131}I MIBG imaging and urinary VMA.

Results: Neuroblastoma patients were 15 boys, and 15 girls. All were younger than 16 years. There were 6 patients in stage III, and 24 in stage IV according to Evans stages. Three patients received 1 course of ^{131}I MIBG, 7: 2 courses, 16: 3 courses, 4: 4 courses. Three out of thirty (10%) of the children showed disease progression, 1/30 (3.3%) showed no response. The rest showed varying degrees of response from stable disease in 2/30 (6.7%). Partial response in 18/30 (60%), and complete response in 6/30 (20%). At 2 years, 17/30 (56.7%) are still alive and (13/30) are dead, 2 of them died of medical causes not related to Neuroblastoms. The median performance status as measured by Karnofsky index markedly improved post MIBG therapy: 80% versus 60% pretherapy(p <0.001). The median body weight significantly increased after therapy: 34 kg versus 27kg pretherapy (p <0.05).

Conclusion: ^{131}I MIBG therapy at a dose of 100 mci is a safe and effective line of therapy in advanced Neuroblastoma.

Key words: *Neuroblastoma, and MIBG: Meta-iodobenzylguanidine.*

INTRODUCTION

Neuroblastoma is a malignant tumour of the sympathetic nervous system occuring most frequently in early childhood. Different factors affect the prognosis of neuroblastoma: which includes age, stage, site of primary tumour, metastases, VMA, serum ferritin, histology and N-myc amplification **[27,21]**. Stages I and II neuroblastoma are reported to be treated with complete excision with a 2 years survival rate of 90%, while stages III and IV are treated with preoperative chemotherapy followed by surgery and high dose chemotherapy, then bone marrow transplantation and radiotherapy **[27]**. After an initial response rate of 80% with the above therapy most children relapse, likely due to drug resistance with a 5 years survival rate of 10-20% **[19]**.

New approaches in therapy of neuroblastoma including targeting of radionuclides by monoclonal antibodies and MIBG are reported **[6,9,18]**. MIBG is now a well established examination in diagnosis and follow up of neuroblastoma **[8]**. In 1981, MIBG was clinically introduced in the treatment of tumours derived from the neural crest **[23]** through an active uptake-1 mechanism at the cell membrane and storage granules in the cytoplasm. The high sensitivity and excellent specificity of MIBG imaging led to its use in therapy of neuroblastoma **[9]**. High selective tumour uptake and retention of MIBG is a prerequisit for succesful treatment targeting both in the primary tumour and distant metastases **[9]**. ^{131}I MIBG was used in therapy of neuroblastoma with varying degrees of response **[1-3,5,9-12,15,16,25]**. Criteria of evaluation of MIBG therapy response was suggested as: CR (no evidence of tumour volume), PR (> 50% reduction of tumour volume), SD (< 50% reduction or no change in tumour volume) and PD increasing disease **[9]**.

DeKraker et al. in 1995 used ^{131}I MIBG for treatment of unresectable localized tumours, stages III and IV and recurrent neuroblastoma. They reported that multiple MIBG courses resulted in a rapid and high response rate with lit-

tle toxicity [4]. One of the largest studies before 1991, was conducted in Amsterdam by Shapiro et al. [22] on 53 neuroblastoma patients over an 8 years period, reported CR in 7 patients, PR in 29 patients with an objective response rate of 57% (2-38 months follow up). Troncone et al. [14] in a multicentric German study on 47 patients of advanced neuroblastoma reported an objective response of 47% in contrast to only 19% reported by Garaventa et al. [5] using low dose MIBG therapy.

After failing of conventional chemotherapy and radiotherapy, 131I MIBG as a second line was used in different centers in Europe and USA starting from 1991 with varying degrees of objective response ranging from 0-100% [1-3,9-13,15-17,25]. With an overall objective response of 35%. These results were encouraging taking in consideration that most of the patients were stage IV, heavily pretreated and after failure of other treatment modalities. However valuable palliation, improved quality of life and good tolerance to MIBG therapy as compared to chemotherapy were observed.

Both MIBG therapy and patients isolation were reported to be well tolerated by children. The most frequent side effects met were isolated thrombocytopenia [10] and severe bone marrow depression especially in patients with bone marrow infiltration. Occasional deterioration in renal functions [26] especially in patients previously receiving Cisplatin and Ifosfamide. One patient was reported to develop acquired hypertensive crisis [24].

PATIENTS AND METHODS

Between June 1996 and August 1998, 30 neuroblastoma patients diagnosed at the Paediatric Oncology Unit of the National Cancer Institute (NCI), Cairo University, Egypt were included in ;the present study with a minimal follow up of 2 years. They were children with Evans stage III and IV who failed after initial successful therapeutic modalities. MIBG was given, as a second line therapy, to patients younger than 16 years with performance status >30% (K.I.).

They were 15 boys and 15 girls. The youngest child was 1 year old, the eldest 15 years old, with a median age of 5 years. Clinical presentation and Evans stages are summarized in table (1).

VMA was elevated in 27/30 patients (90%) with a median of 250 microgm/mgm creatinine. Table (2) shows the number of courses of 131I MIBG given to patients in the present study.

To prevent uptake of 131I 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 131I-MIBG therapy. A fixed dose of 100 mci 131I MIBG was administered over a 4 hours infusion, using a lead-shielded infusion pump. This dose was repeated at 4 weeks interval for 2-3 courses.

Patients were isolated in a private room for 4-6 days and were injected with dexamethasone at a dose of 8 mg/m2, then hostacorten 60 mg/m2 orally for 7 days to guard against laryngeal aedema 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. Assesment of response was done pre and post-therapy at the end of all courses by. 131I MIBG scintigraphy, bone scan, CT scan of the primary tumour, bone marrow aspiration and VMA level estimation.

Criteria of response of 131I MIBG therapy were as follows (Hoefnagel et al., [10]):

- Complete response (CR): >90% decrease in tumour volume.
- Partial response (PR): 50-90% decrease in tumor volume.
- Stationary Disease (SD): <50% decrease in tumour volume.
- No response (NR): no change in the size of the tumour.
- 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 survival Kaplan Meyer's method was used.

RESULTS

Both performance status and body weight improved significantly after MIBG therapy (Table 3). K.I. was 60% and 80% for pre and post-therapy respectively. Also it was noticed that the median body weight was 27kg before treatment compared to 34kg after treatment.

The response rate of patients in showing varying degrees. An objective response was found in 86.7% concerning the primary relapsed tumours. A complete response was found in 6, a

partial response in 18 patients. On the other hand, looking at the patients with metastases, the results of the second line ^{131}I-MIBG treatment was as follows (Table 4):

- 2 patients showed CR.
- 8 patients showed PR.
- 2 patients showed SD.
- 1 patient showed NR.
- 3 patients showed DP.

i.e. 12/16 (75%) of patients presenting with distant metastasis showed objective response. The encountered side effects were: transient abdominal distension in 20/30 patients (66.6%) due to electrolyte imbalance. This could be properly managed. Myelosuppression was found in 21/30 patients (70%), and severe haemorrhage in 1/30 patient which necessitated the stopping of MIBG therapy.

At 2 years post-diagnosis, 17/30 of patients are still alive (56.7%), and the other 13 patients (43.3%) are dead. On the other hand, Fig (1) reveals that the total actuarial survival of the children of the present study at one year was 81% and at two years was 58%.

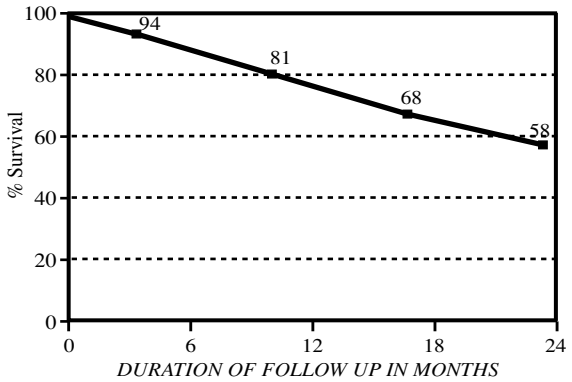

Fig. (1): Total actuarial survival of the study group.

Table (1): Clinical picture and evans stage of neuroblastoma patients receiving second line MIBG therapy.

Item	No. of paticent	%
Primary tumour:		
Thoracic	7	23.3
Abdominal	25	83.3
Metastases:		
Lymph nodes	15	50
Bone marrow	15	50
CNS	5	16.6
Bone	11	36.7
Soft tissue	4	13.3
Bran	2	6.7
Stages:		
III	6	20
IV	24	80

Table (2): No. of courses of second line MIBG therapy given to neuroblastoma patient.

No. of courses	No. of patients	%
1 course	3	10
2 courses	7	23.3
3 courses	16	53.3
4 courses	4	13.3

Table (3): General condition as sown by performance status measured by karnofsky index (K.I.) and pre- and post-therapy body weight.

General Condition / MIBG Therapy	Performance status As measured by median K.I. (%)	Median body weight (Kg)
Pre-therapy	60	27
Post-therapy	80	34
P value	<0.001	= 0.02

Table (4): Response rate of second line MIBG therapy.

Response rate	Total No. of responders		Patients with metastasis	
	No. of patients (total no. =30)	Percentage	No.	%
CR	6	20	2/6	33.3
PR	18	60	8/18	44.4
SD	2	6.7	2/2	100
NR	1	3.3	1/1	100
DP	3	10	3/3	100

Table (5): Comparative results of 131I MIBG therapy in the present study and other studies.

Center	No. of patients	CR	PR	SD	PD	Objective response %
NKI Amsterdam [14,15]	66	7	29	18	9	57
Frankfurt Univ. [16]	15	0	9	1	9	60
Tubingen Univ. [17]	25	4	6	6	0	62.5
Other German centers [17]	20	1	3	8	0	33.3
France Multicenter [18]	26	0	0	10	16	0
Genova and Brescia [19]	43	2	5	23	12	16.7
Royal Marsden, UK [20]	5	1	1	0	0	100
UKCCSG Multicenter [20]	25	0	8	9	7	33.3
Gemelli, Rome [21]	14	2	3	5	2	41.7
Michigan Univers. [22]	14	0	1	3	10	7.1
INT, Milan [23]	7	0	2	2	3	28.6
UCSF, San Francesco [24]	11	0	2	2	7	18.2
Turin Univers. [24]	5	0	1	1	3	20
Total	276	17	70	88	74	34.9
The present study	30	6	18	*3	3	80

* the three cases included 2 SD and 1 NR

DISCUSSION

131I MIBG proved to be effective as a second line therapy in advanced stages of neuroblastoma (III and IV), unresectable localized tumours and in recurrent neuroblastoma. Multiple courses resulted in rapid and high response rate with little toxicity [4]. It was reported to cause valuable palliation and improvement of quality of life with good tolerance as compared to chemotherapy.

Table (5) compares the results of different investigators including the present study. The objective response rate in the present study (84%) is higher than most other figures reported in the literature. The patients achieving PR (60%) is higher than the figure obtained by Hoefnagel et al. of 44% in a study of 66 patients [10]. This can be attributed to: a) higher doses used in our study with a higher number of courses. Twenty of 30 patients (66.6%) received 3 or more courses, and each was at least 100 mci [10]. b) most of the patients had a favourable histology irrespective of their recurrence [2,13,15,16].

The improved performance status as evaluated by Karnofsky index and body weight post-131I MIBG therapy is in agreement with other studies in the literature. The main side effects of myelosuppression of 70% was found to be higher than that reported by Hoefnagel et al. [10] which was 26.4%. Abdominal distension occuring in 20/30 patients (66.6%) might be attributed to the electrolyte imbalance and was easily managed.

The response of distant metastsais to 131I MIBG therapy was found to be high, with 12/16 patients (75%) showing objective response (including cases with stationary disease) and 10/16 patients (60%) showing CR or PR, all with a better performance status. This is in accordance with Hoefnagel et al. [10,11] and Troncone et al. [24] who reported that MIBG therapy provided valuable palliation and improved quality of life for their neuroblastoma patients.

The Survival of patients is considerable as 17/30 (56.7%) are still alive 2 years following diagnosis, 13/30 (43.3%) are dead. Two of these patients died of causes other than the tumour (severe haemorrhage and hepatitis).

In conclusion 131I MIBG at a dose of 100 mci is a safe and effective and well tolerated second line of therapy in advanced, refractory and recurrent neuroblastoma. Using it as a first line of therapy is recommended.

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