ABSTRACT

Introduction: Neuroblastoma, a neoplasm of the sympathetic nervous system, is the second most extra-cranial malignant solid tumor of childhood. Many therapeutic strategies have evolved over the last 20 years, based upon work by international cooperative groups and smaller cohort studies. Novel therapies to improve initial disease response and treatment of minimal residual disease are required to improve survival for these children with high-risk neuroblastoma. Radio-labeled MIBG therapy has been tried in the treatment of advanced stage 3&4 neuroblastoma in an attempt to improve patients' outcome. The use of radio-labeled MIBG to treat neuroblastoma has arisen from the high sensitivity and specificity of in-vivo MIBG imaging for detection of primary and metastatic tumors.

Aim of the Work: To determine the impact of MIBG therapy on neuroblastoma patients' outcome and its impact on their quality of life.

Patients and Methods: Thirty pediatric patients with stage 4 pathologically proven neuroblastoma are included in this study. Eighteen of the study patients (60%) were males and 12 (40%) were females. All the patients had partially responsive tumor to first-line therapy ± surgery. 131-I MIBG doses ranged from 100 to 150mCi with number of courses ranged from 1-7 according to response and toxicity.

Results: Two patients achieved complete remission (CR) and were still disease-free after 64 & 69 months. Nine patients showed partial remission (PR) to 131-I MIBG, all the nine patients were alive at 16-57 months (mean 30.6 months) among whom seven were alive with stable disease and two patients were alive with progressive disease (PD) at the end of study. Eighteen patients remained stable after 131-I MIBG therapy, among them six were alive with PD and four were alive with stable disease at the end of study, while the remaining eight patients died. The last patient developed PD and died within 15 months. The 5 years event free survival (EFS) was 48.2% and the overall survival (OS) was 69%.

Conclusion: We concluded that 131-I MIBG therapy has favorable therapeutic effect for advanced neuroblastoma patients. Controlled clinical trials should be considered to evaluate the true potential of 131-I MIBG therapy.

Key Words: MIBG therapy – Advanced neuroblastoma.

INTRODUCTION

Neuroblastoma is the most common solid extra cranial malignancy in children younger than 15 years. It accounts for 8-10% of all childhood cancers and 15% of cancer deaths in children [1]. Although this tumor is chemo- and radio-sensitive, it is prone to relapse after initial induction of remission. Stage 1 and 2 tumors can be cured with surgery alone, whilst stage 3 tumors require preoperative chemotherapy. Sixty percent of neuroblastomas in children are diagnosed in stage 4, of whom many have biological markers of poor prognosis, such as MYCN amplification or 1p deletion [2]. One of the major goals of cancer treatment is to develop therapies affecting cancer cells while causing little or no damage to the normal counterparts. In this perspective, numerous attempts have been made to bind anti-tumor compounds or radioactive isotopes to molecules specifically taken up by tumor cells. One example of these molecules is meta-iodobenzylguanidine (MIBG), a norepinephrine analogue which is taken up by organs rich in adrenergic innervation and/or
catecholamine excretion. Therefore, I-131 radio-labeled MIBG allows successful imaging of these organs and neuroectodermally derived tumors, such as neuroblastomas, pheochromocytomas, paragangliomas, medullary thyroid carcinomas, carcinoid tumors and Merkel cell skin tumors. The use of radio-labeled MIBG to treat neuroectodermally derived tumors have arisen from the high sensitivity and specificity of in-vivo MIBG imaging for detection of primary and metastatic tumors. Radio-labeled MIBG therapy is most commonly used in the treatment of neuroblastoma, which is a high grade malignancy of childhood [3]. 131-I MIBG was initially reserved for palliation of patients with recurrent disease. However, clinical trials evaluating the role of 131-I MIBG as a first line drug, either as a single agent, or in combination with chemotherapy or myeloablative treatment, or in consolidation treatment has been performed with mixed results and significant potential side effects. The response rates varied between 20% and 60% in newly diagnosed and relapsed or refractory patients [4-9]. Despite all this information, the precise role of 131-I MIBG in the overall therapeutic strategy of neuroblastoma is far from being defined. In particular, it is still unclear whether 131-I MIBG might improve the tumor response of patients who did not achieve complete remission with conventional therapy and are therefore predisposed to disease progression and death. We conducted this retrospective study to present the experience of the National Cancer Institute, Cairo, Egypt of 131-I MIBG therapy in neuroblastoma and to determine the impact of MIBG therapy on patients’ outcome and its impact on their quality of life. This study has been approved by the NCI ethics and research committee.

**PATIENTS AND METHODS**

The study included 30 pediatric patients treated and followed-up at the National Cancer Institute (NCI), Cairo University between March 1998 and June 2004.

*All patients underwent the following pretreatment evaluation:*

- Full clinical examination.
- Complete blood count, liver and kidney functions.
- Bone marrow aspirate and trephine biopsy.
- Markers: Neurone specific enolase, serum ferritin, vanillylmandelic acid (VMA) and lactate dehydrogenase.
- CT abdomen, CT of primary tumor and CT chest.
- Bone scan and diagnostic MIBG.
- Shimada histology and MYCN status.

All patients were stage 4 with confirmed histopathology of neuroblastoma. Eighteen of the study patients (60%) were males and 12 (40%) were females. Their age ranged from 2 years to 11 years, with a mean of 5.6 years. Frequencies of the disease primary sites were as follows: 21 (70%) patients with supra-renal neuroblastoma, 5 (16.6%) retro-peritoneal, 4 (13.6%) para-vertebral. Bone deposits were detected in 26 patients. Hepatic deposits were present in 5 patients and brain metastasis was present in one of them. All patients received high risk neuroblastoma protocol, which comprised 2 courses of etopside 200mg/m$^2$ d1-d3, carboplatin 600mg/m$^2$ d1 only, and 2 courses of CADO (vincristine1.5mg/m$^2$ d1, d5, doxorubicin 60mg/m$^2$ d5 and cyclophosphamide 300mg/m$^2$ d1-d5) followed by surgery and 2 courses of etopside/carboplatin and 2 courses of CADO.

Evaluation of response to 4 courses of chemotherapy was done for all patients, those who had progressive disease or incomplete surgical resection at the level of primary tumor and/or metastatic lesions clearly uptaking 131-I MIBG (no more than four lesions) with no evidence of bone marrow infiltration. Further eligibility criteria for 131-I MIBG therapy included normal CBC, liver and kidney functions.

**Patient preparation before 131-I MIBG therapy:**

1- Reviewing diagnostic investigations i.e. CT, MRI 131-I MIBG diagnostic scan & bone scan.
2- CBC, LFT, KFT were done one day before therapy.
3- Measuring level of tumor markers (venyl mandelic acid VMA, homovanillic HVA in urine), serum neurone specific enolase NSE.
4- Reviewing recent bone marrow aspiration or biopsy to exclude marrow infiltration.
5- Thyroid gland uptake of radioiodine was blocked by oral administration of 2-3mg/kg/day of Lugol’s Iodine solution (saturated solution of KI 10%) given for 3 days before and 7 days after 131-I-MIBG infusion.

131-I MIBG therapy:

The administered doses of 131-I MIBG ranged from 100mCi for children weighing less than 20kg, up to 150mCi for children weighing more than 20kg. Specific activity ranged from 1.4 to 2.3 GBq mg⁻¹ (mean 1.8). 131-I MIBG dose was injected in 100ml saline or 100ml 5% dextrose over 45 minutes. Close relatives actively participated in nursing care were provided with digital pocket dosimeter for radiation exposure monitoring. Patients were discharged usually when the exposure rate at 1 meter is less than 30mR/hr. Once discharged, they were checked weekly clinically and through laboratory tests for hematological indices, kidney & liver functions to monitor any toxicity. Any toxic effects attributable to 131-I MIBG therapy were reported. Assessment of primary tumor & metastasis response was done after the third 131-I MIBG therapy course unless evidence of progressive disease or toxic side effects had occurred. In case of either disease improvement or stability after the third 131-I MIBG course, additional courses with an interval of 4-6 weeks between courses were administered.

Evaluation of tumor response:

**Tumor response was defined as follows:**

1- Complete response (CR), disappearance of primary tumor and of all metastatic lesions with normalization of urine catecholamines.

2- Very good partial response (VGPR), >90% volume reduction of the primary tumor with clearing of all measurable metastatic lesions with the exception of residual changes at skeletal scintigraphy, normalization of urine catecholamines.

3- Partial response (PR), >50% volume reduction of the primary tumor and of all measurable metastatic lesions.

4- Stable disease (SD), <50% reduction but <25% increase in any existing lesion; progressive disease (PD), increase >25% of any measurable lesion or appearance of a new lesion [10].

Response was evaluated 3-4 weeks following the third 131-I MIBG course by means of CT scan, and urinary catecholamines.

**Statistical methods:**

Data management, analysis and graphs were performed using Statistical Package for the Social Sciences SPSS version 13. Survival was calculated using the Kaplan-Meir’s method [20].

**RESULTS**

All the thirty patients included in this study were stage 4 disease who achieved partial response with first-line therapy. Ten of them (33.3%) underwent partial surgical resection. Scintigraphy performed before 131-I MIBG therapy was positive at the primary site and metastatic lesions: Bone deposits (26 patients), hepatic deposits (5 patients) and brain metastases (1 patient). Table (1) summarizes the patients’ data. Two patients received one 131-I MIBG course of therapy, 4 received two courses, 13 received three courses, one received four courses, two received five courses, six received six courses and two received seven courses. Intervals between courses ranged from 4 to 6 weeks. Two patients (6.7%) (cases no. 18,19) achieved CR (clearing of the primary tumor and two bone lesions) and were still alive disease-free after 64 & 69 months. Nine patients (30%) showed PR to 131-I MIBG therapy involving the primary tumor (only the primary tumor) in 5 cases (cases no. 1,8,12,23,29), together with bone lesions in 3 patients (cases no. 4,14,20) and together with hepatic lesion in one patient (case no. 17). All the nine patients are alive at 16-57 months (mean 30.6) among whom seven were alive with stable disease (cases no. 4,12,14,17,20,23,29) and two patients were alive with progressive disease (cases no. 1,8) at the end of study. Eighteen patients (60%) remained stable after 131-I MIBG therapy. The 5-year EFS was 48.2% (Fig. 1) and overall survival was 69% (Fig. 2) with follow-up period of 8-69 months (median 22 months). Among them six were alive with PD (cases no. 2,5,7,11,13,15) at 10-23 months (mean 18.3) and four were alive with stable disease (cases no. 3,16,21,30) at 17-25 months (mean 26.5) (Fig. 4 A,B), while the remaining eight patients died. The last patient (case no. 22) developed PD and died within 15 months (Fig. 3 A,B). We noticed marked improvement in pain in 22 (84.5%) patients out of the 26 patients with
bone metastasis. Twenty-two patients out of the 30 (73.3%) patients included in this study showed better quality of life in the form of pain relief, less treatment burden, no toxic effects of therapy as well as partially relieving the psychological burden of children and parents.

Table (1): Characteristics and outcome of 30 patients with stage 4 neuroblastoma.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex, age (years)</th>
<th>Primary tumor site</th>
<th>Surgery after 1st line chemo</th>
<th>VMA &amp; HVA</th>
<th>131-I MIBG therapy courses</th>
<th>Response after 3rd MIBG course</th>
<th>Clinical course and outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M, 11</td>
<td>Lt. adrenal</td>
<td>No</td>
<td>Elevated</td>
<td>4 courses</td>
<td>PR</td>
<td>Alive 23 months PD</td>
</tr>
<tr>
<td>2</td>
<td>M, 4</td>
<td>Retro-peritoneal</td>
<td>No</td>
<td>Elevated</td>
<td>3 courses</td>
<td>SD</td>
<td>Alive 22 months PD</td>
</tr>
<tr>
<td>3</td>
<td>F, 8</td>
<td>Para-vertebral</td>
<td>Partial resection</td>
<td>Elevated</td>
<td>3 courses</td>
<td>SD</td>
<td>Alive 25 months SD</td>
</tr>
<tr>
<td>4</td>
<td>F, 2</td>
<td>Retro-peritoneal</td>
<td>No</td>
<td>Elevated</td>
<td>6 courses</td>
<td>PR</td>
<td>Alive 31 months SD</td>
</tr>
<tr>
<td>5</td>
<td>M, 10</td>
<td>Rt. adrenal</td>
<td>No</td>
<td>Elevated</td>
<td>2 courses</td>
<td>SD</td>
<td>Alive 23 months PD</td>
</tr>
<tr>
<td>6</td>
<td>M, 2</td>
<td>Lt. adrenal</td>
<td>No</td>
<td>Elevated</td>
<td>1 course</td>
<td>SD</td>
<td>Dead 12 months PD</td>
</tr>
<tr>
<td>7</td>
<td>M, 4</td>
<td>Rt. adrenal</td>
<td>No</td>
<td>Elevated</td>
<td>3 courses</td>
<td>SD</td>
<td>Alive 19 months PD</td>
</tr>
<tr>
<td>8</td>
<td>M, 9</td>
<td>Rt. adrenal</td>
<td>No</td>
<td>Elevated</td>
<td>5 courses</td>
<td>PR</td>
<td>Alive 18 months PD</td>
</tr>
<tr>
<td>9</td>
<td>M, 11</td>
<td>Rt. adrenal</td>
<td>No</td>
<td>Elevated</td>
<td>3 courses</td>
<td>SD</td>
<td>Dead 13 months PD</td>
</tr>
<tr>
<td>10</td>
<td>M, 9</td>
<td>Para-vertebral</td>
<td>No</td>
<td>Elevated</td>
<td>2 courses</td>
<td>SD</td>
<td>Dead 11 months PD</td>
</tr>
<tr>
<td>11</td>
<td>F, 4.5</td>
<td>Rt. adrenal</td>
<td>No</td>
<td>Elevated</td>
<td>3 courses</td>
<td>SD</td>
<td>Alive 19 months PD</td>
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<tr>
<td>12</td>
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<td>Lt. adrenal</td>
<td>Partial resection</td>
<td>Elevated</td>
<td>6 courses</td>
<td>PR</td>
<td>Alive 16 months SD</td>
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<tr>
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<td>Lt. adrenal</td>
<td>No</td>
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<td>3 courses</td>
<td>SD</td>
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<tr>
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<td>Elevated</td>
<td>5 courses</td>
<td>PR</td>
<td>Alive 28 months SD</td>
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<tr>
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<td>No</td>
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<td>3 courses</td>
<td>SD</td>
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<tr>
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<td>Retro-peritoneal</td>
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<td>Elevated</td>
<td>3 courses</td>
<td>SD</td>
<td>Alive 40 months SD</td>
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<td>Rt. adrenal</td>
<td>Partial resection</td>
<td>Elevated</td>
<td>6 courses</td>
<td>PR</td>
<td>Alive 42 months SD</td>
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<tr>
<td>18</td>
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<td>Lt. supra-renal</td>
<td>Partial resection</td>
<td>Elevated</td>
<td>7 courses</td>
<td>CR</td>
<td>Alive 64 months CR</td>
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<tr>
<td>19</td>
<td>F, 2</td>
<td>Rt. adrenal</td>
<td>Partial resection</td>
<td>Elevated</td>
<td>7 courses</td>
<td>CR</td>
<td>Alive 69 months CR</td>
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<tr>
<td>20</td>
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<td>Lt. adrenal</td>
<td>Partial resection</td>
<td>Elevated</td>
<td>6 courses</td>
<td>PR</td>
<td>Alive 57 months SD</td>
</tr>
<tr>
<td>21</td>
<td>M, 3.5</td>
<td>Rt. adrenal</td>
<td>No</td>
<td>Elevated</td>
<td>3 courses</td>
<td>SD</td>
<td>Alive 24 months SD</td>
</tr>
<tr>
<td>22</td>
<td>M, 4</td>
<td>Rt. adrenal</td>
<td>Partial resection</td>
<td>Elevated</td>
<td>2 courses</td>
<td>PD</td>
<td>Dead 15 months PD</td>
</tr>
<tr>
<td>23</td>
<td>M, 11</td>
<td>Rt. adrenal</td>
<td>Partial resection</td>
<td>Elevated</td>
<td>6 courses</td>
<td>PR</td>
<td>Alive 37 months SD</td>
</tr>
<tr>
<td>24</td>
<td>M, 3</td>
<td>Lt. adrenal</td>
<td>No</td>
<td>Elevated</td>
<td>1 course</td>
<td>SD</td>
<td>Dead 8 months PD</td>
</tr>
<tr>
<td>25</td>
<td>F, 3</td>
<td>Retro-peritoneal</td>
<td>No</td>
<td>Elevated</td>
<td>2 courses</td>
<td>SD</td>
<td>Dead 13 months PD</td>
</tr>
<tr>
<td>26</td>
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<td>Lt. adrenal</td>
<td>No</td>
<td>Elevated</td>
<td>3 courses</td>
<td>SD</td>
<td>Dead 15 months PD</td>
</tr>
<tr>
<td>27</td>
<td>M, 11</td>
<td>Lt. adrenal</td>
<td>No</td>
<td>Elevated</td>
<td>3 courses</td>
<td>SD</td>
<td>Dead 9 months PD</td>
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<tr>
<td>28</td>
<td>M, 3</td>
<td>Para-vertebral</td>
<td>No</td>
<td>Elevated</td>
<td>3 courses</td>
<td>SD</td>
<td>Dead 11 months PD</td>
</tr>
<tr>
<td>29</td>
<td>M, 9</td>
<td>Retro-peritoneal</td>
<td>Partial resection</td>
<td>Elevated</td>
<td>6 courses</td>
<td>PR</td>
<td>Alive 24 months SD</td>
</tr>
<tr>
<td>30</td>
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<td>Rt. adrenal</td>
<td>No</td>
<td>Elevated</td>
<td>3 courses</td>
<td>SD</td>
<td>Alive 17 months SD</td>
</tr>
</tbody>
</table>


Fig. (1): Event free survival of 30 patients with stage IV neuroblastoma.

Fig (2): Overall survival of 30 patients with stage IV neuroblastoma.
Fig. (3-A,B): A. Pre-MIBG therapy scan anterior (Left) and posterior (right) images showing Rt. Supra-renal neuroblastoma. B. Post MIBG therapy scan anterior (Left) and posterior (right) images showing progression of the disease in the form of increase in the primary lesion appearance of new MIBG avid dorsal and mid Lt. Upper femoral lesion (arrowed) (Case 22).

Fig. (4-A,B): A. Pre- MIBG therapy scan (Left) and CT cut (Right) showing Rt. Supra-renal mass. B. Post therapy MIBG scan (left) and CT cut (right) showing no change in size and activity of the Rt. Supra-renal mass after 7 courses of MIBG therapy (Case 21).
DISCUSSION

Long-term survival of children with inoperable or disseminated neuroblastoma diagnosed after the age of 1 year remains largely unsatisfactory, mainly because chemotherapy treatment usually fails to eradicate the disease [11-13]. Thus, alternative therapies are being trialed for the benefit of increasing long term survival and improving quality of life. Radio-labeled benzylguanidine with Iodine 131 has been used in the treatment of neural crest tumors and seemed suitable due to its physical characteristics. The radiation emitted from 131-I MIBG proved to be effective to induce damage of large tumor lesions [14]. 131-I MIBG therapy for neuroblastoma has been used since the late 1980 and demonstrated objective tumor responses in 20-60% of patients failing to respond to chemotherapy treatment protocols [15-17]. In addition, significant pain relief was noticed even in patients who did not exhibit objective responses [16]. Similarly in the present study, we noticed marked improvement in pain in 22 (84.5%) patients out of the 26 patients with bone metastasis. And a better quality of life was achieved in the form of pain relief, less treatment burden, no toxic effects of therapy as well as partially relieving the psychological burden of the children and their parents mostly due to stopping the chemotherapy. Recently, attempts were being made to evaluate whether 131-I MIBG given as front-line therapy may improve the outcome of these patients without causing excessive toxicity [18,19]. To our knowledge, no prospective study has been carried out so far to evaluate the true potential value of MIBG therapy and to identify the group of patients who may profit best from this treatment modality. The difficulties in design of such studies include the high cost of the drug, many centers do not possess the facilities to deliver this treatment to young patients, and the burden of keeping patient in a radiation protected environment with limited parental contact extended for few days. In the present study, two patients (cases no. 18,19) achieved CR (clearing of the primary tumor) in 5 cases (cases no. 1,8,12,23, 29), together with bone lesions in 3 patients (cases no. 4,14,20) and together with hepatic lesion in one patient (case no. 17). All the nine patients are alive at 16-57 months (mean 30.6) among whom seven were alive with stable disease (cases no. 4,12,14,17,20,23, 29) and two patients were alive with progressive disease (cases no. 1,8) at the end of study. Eighteen patients remained stable after 131-I MIBG therapy. Among them six were alive with PD (cases no. 2,5,7,11,13,15) at 10-23 months (mean 18.3) and four were alive with stable disease (cases no. 3,16,21,30) at 17-25 months (mean 26.5) (Fig. 4 A,B), while the remaining eight patients died. The last patient (case no. 22) developed PD and died within 15 months (Fig. 3 A,B). The 5-year EFS was 48.2% and overall survival was 69% with follow-up period of 8-69 months (median 22 months). Garaventa, et al. 1993 [11], studied 31 patients treated with 131-I MIBG after disease relapse or progression. They reported that the rate and degree of responses were lower in the presence of bulky disease, a high number of MIBG-positive lesions, long duration of previous therapy and overt bone marrow infiltration. In 1999, Garaventa, et al. [21], published their work on MIBG therapy in children with high-risk neuroblastoma who responded to first-line therapy without achieving CR, provided that the residual primary tumor and/or metastase(s) were clearly MIBG avid. They reported that MIBG therapy showed very good partial response in 4/13 patients with stage 3 neuroblastoma, 1 patient showed disease progression and 8 patients showed stable disease. Regarding stage 4 patients, 1/30 patients showed CR, 10 patients showed PR, 15 patients had no response to MIBG therapy and 4 patients showed progressive disease. They stated the 5-year event-free survival (EFS) of stage 3 neuroblastoma was 92% (±0.07) and that of stage 4 was 40% (±0.08). Another study by Matthey, et al. 2003 [22] studied the correlation of early response to therapy by MIBG scan, using a semiquantitative scoring method, with the end induction response and EFS rate for stage 4 neuroblastoma. Seventy-five children older than 1 year and with stage 4 neuroblastoma had 131-I MIBG scans at diagnosis, after 2 and 4 cycles of induction therapy, and before autologous stem-cell transplantation. MIBG scores were then correlated with overall pre-transplantation response, bone marrow response, and EFS. The pre-transplantation response rate was 81%, and the 3-year EFS rate was 32%. The median relative MIBG scores...
after 2, 4, and 6 cycles were 0.5, 0.24, and 0.12, respectively. The probability of having a complete response or very good partial response before transplantation was significantly higher if the relative score after 2 cycles was ≤ 0.5, or, if after 4 cycles, the relative score was ≤ 0.24. Patients with a relative score of ≤ 0.5 after 2 cycles or a score of ≤ 0.24 after 4 cycles had an improved EFS rate (p = .053 and .045, respectively). They concluded that semiquantitative MIBG score early in therapy provides valuable prognostic information for overall response and EFS, which may be useful in tailoring treatment [22]. In this study, 2 patients received one 131-I MIBG course of therapy, 4 received 2 courses, 13 received three courses, 1 received 4 courses, 2 received 5 courses, 6 received 6 courses and 2 received 7 courses. Intervals between courses ranged from 4 to 6 weeks. The dose of MIBG ranged from 100 to 150mCi with the number of courses ranging from 1-7 according to response and toxicity. The aim of a recent trial phase 1 study by Matthay, et al. 2009 [23], was to determine the maximum-tolerated dose of 131-I-MIBG in two consecutive infusions at a 2-week interval, supported by autologous stem cell rescue (ASCR) 2 weeks after the second dose. Twenty-one patients were enrolled in the study at levels 1 to 4, with 18 patients assessable for toxicity and 20 patients assessable for response. Cumulative 131-I-MIBG given to achieve the target RMI ranged from 22 to 50mCi/kg, with cumulative RMI of 3.2 to 8.92Gy. No patient had a dose-limiting toxicity. Reversible grade 3 nonhematologic toxicity occurred in six patients at level 4, establishing the recommended cumulative dose as 36mCi/kg. The median time to absolute neutrophil count more than 500/µL after ASCR was 13 days (4 to 27 days) and to platelet independence was 17 days (6 to 47 days). Responses included two partial responses, eight mixed responses, three stable disease, and seven progressive disease. Responses by semiquantitative MIBG score occurred in eight patients, soft tissue responses occurred in five of 11 patients, but bone marrow responses occurred in only two of 13 patients. They concluded that the lack of toxicity with this approach allowed dramatic dose intensification of 131-I-MIBG, with minimal toxicity and promising activity. A study was done by Mastrangelo, et al. 2001 [24], to determine short-term toxicity and efficacy of a new therapeutic model based on the simultaneous use of multiple drug chemotherapy and specific irradiation using 131-I-MIBG. The study population consisted of 21 patients, from 1 to 8 years of age with good 131-I-MIBG uptake. Sixteen extensively pre-treated patients with refractory or relapsed disease were divided into 2 groups. In Group 1 (9 patients) the basic chemotherapy regimen consisted of cisplatin at the dose of 20mg/m² i.v. per day infused over 2h, for 4 consecutive days; on day 4 Cy 2g/m² i.v. was administered over 2h followed by Mesna. Group 2 (7 patients) was treated with basic chemotherapeutic regimen plus VP16 and Vincristine. VP16 at the dose of 50mg/m² i.v. per day was administered as a 24 h infusion on days 1-3; Vincristine 1.5mg/m² i.v. was administered on days 1 and 6. On day 10 a single dose of 131-I-MIBG (200mCi) with a high specific activity (>1.1 GBq/mg) was administered to both Groups by i.v. infusion over 4-6 hours. A further 5 patients were treated at diagnosis: 2 with the same regimen as Group 1 and 3 with the same as Group 2. Assessment of tumor response was monitored 4-6 weeks after the beginning of combined therapy (CO-TH). Response was defined according to INSS (International Neuroblastoma Staging System) criteria. In the 16 resistant patients, 12 PR, 1 mixed response and 3 SD were obtained. In the 5 patients treated at diagnosis 2 PR, 1 CR and 2 VGPR were observed. No alteration in 131-I-MIBG uptake was observed after the chemotherapy preceding radio-metabolic treatment. The therapeutic results of this pilot regimen of CO-TH resulted in a high percentage of major response after only a single course in both resistant patients and patients treated at diagnosis. It is to be hoped that this suggested novel approach may represent an important route of investigation to improve final outcome in patients with advanced NB.

**Conclusion:**

We concluded that 131-I MIBG therapy has favorable therapeutic effect for advanced neuroblastoma patients after failure of first line therapy and this effect is translated into an overall improved outcome with good quality of life. Further studies are needed to assess the possibility of using the 131-I-MIBG as a front-line therapy, either alone with higher doses or in combination with chemotherapy.
REFERENCES


