

Targeted Therapy with Low Doses of ¹³¹I-MIBG is Effective for Disease Palliation in Highly Refractory Neuroblastoma

Myriam Weyl Ben-Arush MD¹, Ayelet Ben Barak MD¹, Raquel Bar-Deroma DSc², Shifra Ash MD⁴, Gal Goldstein MD⁵, Hanna Golan MD⁵, Haim Houri MD⁵, Dalia Waldman MD⁵, Neta Nevo MD¹, Rachel Bar Shalom MD³, Alison Berniger RN², Alexander Nevelsky MSc², Amos Toren MD PhD⁵, Isaac Yaniv MD⁴ and Abraham Kuten MD²

¹Department of Pediatric Hematology Oncology, Meyer Children's Hospital, ²Division of Oncology, and ³Department of Nuclear Medicine, Rambam Health Care Campus, Haifa, Israel

⁴Department of Pediatric Hematology Oncology, Schneider Children's Hospital of Israel, Petah Tikva, Israel

⁵Department of Pediatric Hematology Oncology, Dana Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel

ABSTRACT: **Background:** Palliative treatment of refractory neuroblastoma remains a significant clinical problem.

Objectives: To retrospectively determine the clinical response to ¹³¹I-MIBG therapy at low doses in patients with refractory neuroblastoma.

Methods: We performed a retrospective chart review of 10 patients with neuroblastoma treated with ¹³¹I-MIBG at Rambam Health Care Campus from 1994 to 2012. Clinical data, number of ¹³¹I-MIBG courses delivered, toxicities, and clinical responses were reviewed. MIBG scan was performed after each course.

Results: Twenty-one courses of ¹³¹I-MIBG were delivered to 10 patients (3 girls, 7 boys). Their mean age was 3.8 years (range 1.5–6 years). All patients received several protocols of chemotherapy including the high dose form. Three patients received three courses of ¹³¹I-MIBG with a minimum of 6 weeks between each course, five patients received two courses, and two patients received only one course. An objective response to the first course was obtained in nine patients and to the second course in six of eight, and in three children who underwent the third course the pain decreased. One patient has no evidence of disease, four are alive with disease, and five died of the disease. No unanticipated toxicities were observed.

Conclusions: Low dose ¹³¹I-MIBG is an effective and relatively non-toxic treatment in neuroblastoma disease palliation. Rapid and reproducible pain relief with ¹³¹I-MIBG was obtained in most of the children. Treatment with systemic radiotherapy in the form of low dose ¹³¹I-MIBG was easy to perform and effective in cases of disseminated neuroblastoma, demonstrating that this primary therapy can be used for palliative purposes.

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KEY WORDS: neuroblastoma, palliation, ¹³¹I-MIBG, radiotherapy

rate to the combination of chemotherapy, surgery, radiotherapy and immunotherapy, a large number of patients will have a recurrence of their disease before or after completion of therapy [2]. Interacting with the characteristic features of neuroblastoma, specific targeting of radiopharmaceuticals may be achieved via the metabolic route (MIBG), via receptor binding (peptides), or via the immunological route (antibodies) [1]. The active uptake mechanism in the cell membrane and neurosecretory storage granules in the cytoplasm of neuroblastoma are responsible for the uptake and retention of ¹³¹I-MIBG, respectively. Although the radiopharmaceutical may be released from the granules, reuptake through this specific mechanism maintains prolonged intracellular concentration [3]. Cumulative results of ¹³¹I-MIBG scintigraphy reported in the literature indicate that more than 90% of neuroblastomas concentrate ¹³¹I-MIBG [4]; the uptake of ¹³¹I-MIBG is tissue specific. This enables the detection of metastases regardless of their localization. Moreover, the prolonged intracellular concentration of ¹³¹I-MIBG at tumor sites, in contrast to normal tissue, has led to the use of this radiopharmaceutical for therapy [5]. ¹³¹I-MIBG has been used with success for radionuclide therapy of neuroblastoma since 1984 [6]. A few authors have published their experiences with higher dose ¹³¹I-MIBG and demonstrated its value as a palliative agent in advanced refractory neuroblastoma [6–8]; however, thrombocytopenia limits repeated use.

Acceptable pain control can be achieved with analgesics in most children, but some patients with skeletal involvement required an alternative method of pain control during the terminal phase of their disease. We report here our experience with low dose ¹³¹I-MIBG for disease palliation in refractory neuroblastoma.

PATIENTS AND METHODS [Table 1]

Patients were eligible to receive more than one course of ¹³¹I-MIBG if they showed objective clinical improvement and generally decreased pain. Information collected for the study included gender, age at diagnosis, stage of disease, response

The choice of treatment for neuroblastoma depends on the stage of the disease, the age of the child, and biological molecular prognostic factors [1]. Despite a high initial response

Table 1. Patient characteristics

No./gender	Age at diagnosis (yrs)	INSS stage at diagnosis	NMYC	Best response prior to ¹³¹ I-MIBG	Disease status
1/M	2.5	4	Unknown	CR	AWD
2/M	3	4	Not amplified	CR	AWD
3/F	7	4	Unknown	SD	DOD
4/M	6	4	Not amplified	PR	NED
5/M	1.5	3	Unknown	SD	DOD
6/M	3	4	Unknown	PD	DOD
7/F	1.5	4	Not amplified	SD	DOD
8/M	3	4	Not amplified	CR	DOD
9/M	5	4	Not amplified	PR	AWD
10/F	6	4	Not amplified	PR	AWD

CR = complete remission, PR = partial response, SD = stable disease, PD = progressive disease, AED = alive with disease, DOD = dead of disease, NED = no evidence of disease

to treatment, and clinical outcome data. Disease stage was assigned according to the International Neuroblastoma Staging System, and NMYC amplification was detected by dual color fluorescence in situ hybridization. Clinical improvement in performance status and pain were recorded after each dose of ¹³¹I-MIBG. Amelioration of pain was measured according to a pain scale questionnaire; well-being status was also measured. Toxicity of therapy was recorded using the National Institutes of Health Common Toxicity Criteria. Blood cell counts were performed once weekly and platelets and blood transfusions were given according to the blood tests. RECIST (Response Evaluation Criteria In Solid Tumors) criteria were used to define disease response to treatment.

Children were hospitalized in isolated rooms in the radiotherapy department. A grandparent stayed with them during the 4 or 5 days of hospitalization for ¹³¹I-MIBG. A fixed dose of 5 mCi/kg (maximum dose 150 mCi) was administered over a 1–2 hour period using a three-way tap system attached to a shielded trolley and an infusion pump. To protect the thyroid from free radioactive iodine, potassium iodide was given orally daily (100 mg for children, 200 mg for adults). If clinical improvement was noted, the treatment was repeated every 6 weeks. The professional team was multidisciplinary and inclu-

ded medical physicists who were responsible for treatment preparation and delivery as well as radiation safety. Children were discharged by a medical physicist according to the radiation dose calculated from exposure measurements at a distance of 2 m.

RESULTS [Table 2]

Between 1994 and 2012, 12 children were referred to Rambam Medical Center for treatment with ¹³¹I-MIBG at a dose of 5 mCi/kg. The children had been treated for refractory neuroblastoma at various institutions in Israel. Ten children were available for the study (2 were lost to follow-up). All the children were symptomatic, due to bone metastases in most of them, and were treated by opiate analgesic medication. The mean follow-up period was 4.7 years (1–18 years).

The patients' mean age was 3.8 years (range 14 months to 7 years); there were 7 boys and 3 girls. Nine patients had stage IV disease and one had stage III. The primary tumor was abdominal in nine cases and posterior mediastinum in one. NMYC was not amplified in six patients and was unknown in four. At diagnosis and during treatment, all the children underwent staging with MIBG scan.

All the children were treated with international protocols (COG, POG or SIOPEN). The first relapse occurred at a median of 29 months (range 3–38). Treatment with ¹³¹I-MIBG was delivered at first relapse in one child, at second relapse in one, at third relapse in one, at fourth relapse in six, and at fifth relapse in one. Several different protocols were delivered after the relapses before the MIBG treatment: topotecan cyclophosphamide was delivered to seven patients, irinotecan and temodal to one patient, carboplatin and etoposide to one, zoledronic acid and cyclophosphamide

Table 2. Anti-tumor response to ¹³¹I-MIBG

Patient no.	First dose of ¹³¹ I-MIBG	Second dose of ¹³¹ I-MIBG	Third dose of ¹³¹ I-MIBG	Clinical response to 1st dose	Pain prior to ¹³¹ I-MIBG	Site of pain	Pain improvement post-first ¹³¹ I-MIBG	Pain improvement post-second ¹³¹ I-MIBG
1	Yes	Yes	Yes	PR	Yes	Extremities, abdomen	Yes	Yes
2	Yes	Yes	Yes	PR	Yes	Extremity	Yes	Yes
3	Yes	No	No	TP	Yes	Extremity	No	No
4	Yes	Yes	No	PR	Yes	Extremity	Yes	Yes
5	Yes	Yes	No	PR	Yes	Extremity	Yes	Yes
6	Yes	No	No	PR	Yes	Back, extremity	Yes	No
7	Yes	Yes	No	PR	Yes	Back, extremity	Yes	Yes
8	Yes	Yes	No	PR	Yes	Extremity	Yes	No
9	Yes	Yes	No	PR	Yes	Extremity	Yes	Yes
10	Yes	Yes	Yes	PR	Yes	Extremity	Yes	Yes

to one, and cyclophosphamide doxorubicin and vincristine to one. Three patients received three courses of ^{131}I -MIBG, five patients received two courses, and two patients received only one course. Of the 21 courses delivered to 10 patients, 19 of 21 were associated with clinical improvement.

Clinical improvement, especially decreased pain and improvement in general status, was observed in all nine children who received two and three courses of ^{131}I -MIBG. MIBG scans showed a decrease in uptake in most of the lesions in three children, while four children had stable disease. One child responded with decreased pain and decreased narcotic use; bone biopsy performed in this child to measure response to treatment showed differentiation [9], but he developed tumor progression immediately after treatment. One patient did not respond to treatment.

Eight children received the second dose. One child with posterior mediastinal tumor had complete response and is now without evidence of disease 17 years after treatment. Two children transiently responded to treatment but died 4 and 9 months after MIBG. One child progressed 2 months after ^{131}I -MIBG and died, and one child has stable disease without treatment.

Three children received the third dose. One is alive with disease but without any pain 6 months after treatment, one is alive with disease 7 years after the third dose and without any further treatment, and one is stable on cyclophosphamide and topotecan 12 months after the last dose of ^{131}I -MIBG.

Toxicity included grade 3 thrombocytopenia in eight children but no episode of life-threatening bleeding or adverse events secondary to anemia or thrombocytopenia. One child is being treated for hypothyroidism.

DISCUSSION

Previous sporadic cases have shown the efficacy of low dose ^{131}I -MIBG in reducing pain in children suffering from refractory neuroblastoma and, consequently, improving their quality of life [10]. No studies have described the role of repeated low doses of ^{131}I -MIBG in diminishing pain and improving quality of life in children afflicted with progressive neuroblastoma. In a phase II study [11] conducted in 53 patients with metastatic or refractory neuroblastoma treated at the Netherlands Cancer Institute, 7 patients entered complete remission and 23 patients had partial remission with durations of 2–38 months. Apart from objective response, the palliative effect of the treatment under these conditions was remarkable, often leading to complete pain relief within days after treatment. The best results were obtained in patients with bulky soft disease. In 1991, the pooled results of a total of 273 neuroblastoma patients treated at major centers indicated an overall objective response rate of 35% [12]. Most of these patients had stage IV, progressive and intensely pretreated disease, and were only treated with

^{131}I -MIBG after other treatment modalities had failed. In addition, ^{131}I -MIBG therapy provided valuable palliation and improved quality of life to most patients [12]. In 2003, Kang and co-authors [13] published the results of targeted radiotherapy with sub-myeloablative doses of ^{131}I -MIBG for disease palliation in highly refractory neuroblastoma. A median dose of 9.5 mCi/kg ^{131}I -MIBG was delivered in 32 courses to 20 patients. Of 17 patients 11 (65%) had tumor-related pain prior to receiving ^{131}I -MIBG. After ^{131}I -MIBG therapy, 9 of 11 patients exhibited a clinical response to treatment and reduction in pain and analgesic drug intake. Seven of eight patients with bone pain responded to treatment, and two of three patients with pain localized to soft tissue had clinical improvement. Altogether, 20 courses were given to 11 patients; 16 of 20 courses were effective but no correlation was observed between pain and total dose of ^{131}I -MIBG.

Bone marrow depression, mainly thrombocytopenia, is the most significant side effect of ^{131}I -MIBG therapy [14]. This is thought to be due to the selective binding of ^{131}I -MIBG to megacaryocytes [15]. The severity of the thrombocytopenia is correlated to the extent of the duration of previous therapy and the presence of massive bone marrow infiltration. Even at higher doses, ^{131}I -MIBG can be administered safely in heavily treated patients [13]. Thyroid hypofunction has been reported in some patients, as in one of our cases [16]. Second malignancies after high doses of ^{131}I -MIBG were reported by Garaventa et al. [17] in a series of 119 children treated for refractory neuroblastoma by ^{131}I -MIBG, and in 3 of 95 patients reported by Weiss et al. [18].

Low dose ^{131}I -MIBG is an effective and relatively non-toxic therapy for neuroblastoma disease palliation. Most patients show subjective improvement in pain and/or performance status. Rapid and reproducible pain relief with ^{131}I -MIBG was obtained in most of the children treated in our institution, avoiding high doses of morphine for long periods. We conclude that treatment with systemic radiotherapy in the form of ^{131}I -MIBG is easy to perform and effective in cases of disseminated neuroblastoma, illustrating that this primary therapy can be used for palliative purposes.

Corresponding author:

Dr. M. Weyl Ben-Arush

Dept. of Pediatric Hematology Oncology, Meyer Children's Hospital, Rambam Health Care Campus, P.O. Box 9602, Haifa 31096, Israel

Phone: (972-4) 854-3002

Fax: (972-4) 854-2007

email: m_benarush@rambam.health.gov.il

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Capsule

Genetic basis for Intellectual and neurological disabilities

Intellectual and neurological disabilities can arise from diverse developmental aberrations. Novarino and group have now determined the genetic basis for one such disorder for a small group of patients. Exome sequencing led to identification of mutations in a kinase *BCKDK* (branched chain ketoacid dehydrogenase kinase) that regulates metabolism of branched-chain amino acids such as valine, leucine, and isoleucine. Mice with homozygous mutations in the *BCKDK* gene showed developmental and neurological abnormalities

resembling those in certain mouse autism models. Analysis of transport mechanisms responsible for carrying amino acids across the blood-brain barrier revealed competition between the branched-chain amino acids and large neutral amino acids. Nutritional supplementation with extra branched-chain amino acids in the diet of mice carrying homozygous mutations in the *BCKDK* gene normalized their phenotype.

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Eitan Israeli

Capsule

Clonal allelic predetermination of immunoglobulin-κ rearrangement

Although most genes are expressed biallelically, a number of key genomic sites – including immune and olfactory receptor regions – are controlled monoallelically in a stochastic manner, with some cells expressing the maternal allele and others the paternal allele in the target tissue. Very little is known about how this phenomenon is regulated and programmed during development. Using mouse immunoglobulin-κ (Igκ) as a model system, Fargo and colleagues demonstrate that although individual hematopoietic stem cells are characterized by allelic

plasticity, early lymphoid lineage cells become committed to the choice of a single allele, and this decision is then stably maintained in a clonal manner that predetermines monoallelic rearrangement in B cells. This is accompanied at the molecular level by underlying allelic changes in asynchronous replication timing patterns at the κ locus. These experiments may serve to define a new concept of stem cell plasticity.

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Eitan Israeli

“It is a truism that almost any sect, cult, or religion will legislate its creed into law if it acquires the political power to do so”

Robert A. Heinlein (1907-1988), American science fiction writer and one of the most influential and controversial authors of the genre in his time

Camel Milk and its Unique Anti-Diarrheal Properties

Reuven Yagil DVM*

*Prof. (emeritus) Reuven Yagil studied veterinary medicine in Holland. He was one of the first lecturers in human physiology in the Faculty of Health Sciences at the Ben-Gurion University of the Negev. He is considered the world expert on camel milk

KEY WORDS: immunoglobulins, protective proteins, Johne’s disease, casomorphine, autism syndrome, Crohn’s disease, retrovirus

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In the past few years there has been an upsurge of global interest in the healing effects of camel milk following the Internet posting by the Food and Agriculture Organization of the United Nations that human consumption of camel milk could generate a billion dollars of income [1]. The healing properties of camel milk were first mentioned in the “Words of The Prophet Mohamed” in the *Surah*, a section of the Koran (Volume 7, Book 71, number 590) [2].

Due to the demand for pasteurization, which negates most of the benefits of camel milk, there is a dearth of clinical trials on the healing effects of camel milk. The few animal studies that have been published provide evidence on its therapeutic activity. This is demonstrated in the article in the present issue of *IMAJ* on the action of camel milk in mice inoculated with *Salmonella enterica* [3].

Among the “protective proteins” in camel milk are lysozyme, lactoferrin, lactoperoxidase, and peptidoglycan recognition protein [4,5]. These properties have anti-diarrheal/antibacterial action as well as high titers of antibodies against rotavirus, and they impact on the immune system. Only human and camel milk have physiologically high concentrations of the enzyme NaGase (N-acetyl-B-glucosaminidase) [6] which in milch cows is an indication of mastitis.

Camel immunoglobulins are a tenth the size of human ones and are highly potent [7]. These properties have been put to use by the Homeland Security Department of the United States government to create biosensors for determining which agent is being used in a biological warfare attack [8].

For hundreds of years camel milk has been used to treat diarrhea even though the identity of the active substance in the milk was not known. The present article offers a new look at two gastrointestinal diseases, with accompanying immunological involvement, that have reached epidemic proportions and which respond to camel milk.

AUTISM SYNDROME

Autism is an autoimmune disease [9] that, surprisingly, attacks the intestines, not the brain [10]. Reactions in the intestines are diarrhea, “leaky gut” syndrome, and the effect on appetite (“picky eater”). The most prominent cerebral symptoms are caused by a malfunction in the formation of amino acids from two caseins in cow milk, beta-casein and beta-lactoglobulin. Instead, a powerful opioid, casomorphine, is formed [11]. This opioid elicits the cerebral symptoms of the autism syndrome. This hypothesis is supported by evidence showing that when dairy products are removed from the diet the “cerebral” symptoms dissipate [12]. This theory emerged when it was found that people with autistic syndrome suffering from diarrhea had normal bowel movements when treated with camel milk as well as improved cerebral symptoms [10]. Camel milk does not contain the two caseins that form casomorphine from cow

milk, so symptoms do not develop, while the active immune system in the camel milk helps ameliorate the autoimmune problems. Animal studies (in laboratory rats) confirmed the above hypothesis when injections of casomorphine caused autism-like symptoms [13]. Therefore, it is probable that the autism syndrome is primarily an autoimmune disease that affects the intestines. Brain damage is secondary at an older age.

CROHN’S DISEASE

It is commonly accepted that Crohn’s disease is an autoimmune disease. However, there are numerous data suggesting that a bovine disorder, Johne’s disease, is associated with Crohn’s disease via a bacterium, *Mycobacterium avium* paratuberculosis. MAP is absorbable by humans because it is not destroyed by pasteurization [14]. This theory was previously discarded but increasing data are prompting a second look.

It is hypothesized that after MAP enters the intestinal tissues it remains there as a saprophyte, becoming active only in the presence of severe emotional stress [15]. Antibodies are then formed to counteract the infection, but as they are too large to penetrate the intestinal tissues they bombard them from the outside, leading to an autoimmune situation. It is therefore theorized that Crohn’s disease is primarily a bacterial infection and secondarily an autoimmune disease.

That MAP plays a role in Crohn’s disease was given credence when it was found that lactating women in Canada suffering from Crohn’s disease secrete

MAP = *Mycobacterium avium* paratuberculosis