^{131}I-MIBG Therapy

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Metaiodobenzylguanidine (MIBG) was developed in the 1980s to be used as an imaging agent for neuroblastoma and other adrenergic tumors to visualize the location and amount of disease in the body. For imaging, MIBG is attached (or radiolabeled) with iodine-123 (^{123}I, a radioactive isotope of iodine) which can act as a tracer to locate cancer throughout the body. Approximately 90% of neuroblastoma (NB) patients will have "MIBG avid" disease.[1] This means that MIBG will accumulate in the neuroblastoma cells in the body and can be detected on a nuclear medicine scan. It will concentrate in neuroblastoma cells that are present as soft-tissue, bone, and marrow disease[2], and will accumulate in cancer cells with or without MYCN amplification, with or without favourable histology and at all risk stages in both newly diagnosed and relapsed disease.[3,4] The MIBG scan is arguably the most important imaging tool for neuroblastoma and is critical to determine the location, extent, response and staging of the disease at the time of diagnosis and throughout the treatment journey.[5,6] However, it is known that MIBG scans can have reduced accuracy when imaging for disease activity in the brain or in small lung metastases.[7]

Therapeutic clinical trials using MIBG as neuroblastoma therapy began in the 1980s and focused on understanding the appropriate dosing for high-risk relapsed and refractory neuroblastoma (phase 1 trials focus on finding the appropriate dose and phase 2 trials examine the response of the disease to the dose determined in the phase 1 clinical trial).[8] When MIBG is used for therapy, and not imaging, it is radiolabeled with iodine-131 (^{131}I, a radioactive isotope of iodine). ^{131}I has a much longer half-life than ^{123}I and delivers a higher dose of radioactivity to the patient. ^{131}I has a physical half life of 8 days, but approximately half of the injected dose of ^{131}I-MIBG is excreted from the body after 24 hours. However, due to the long half life of the isotope, radioactivity from the MIBG bound to the tumor will remain in the body for several weeks. However, ^{123}I-MIBG is superior over ^{131}I-MIBG in providing higher quality images of disease, even with the lower dose of radiation[9] (with a half-life of approximately 13-14 hours).

In a cooperative multi-institutional phase 2 study[10], the largest of its kind, the researchers examined the response rates of MIBG therapy as a singular therapy (or monotherapy) in 164 patients with refractory and relapsed disease at two different dosing levels (12 mCi/kg and 18 mCi/kg). As a follow-up to a prior phase 1 study[11], they also examined short and long term toxicities (side effects), the impact of therapy on particular disease sites, and the safety of a lower dose MIBG therapy (12 mCi/kg) for patients without banked (stored) stem cells. The vast majority of the patients were heavily pretreated, with an average of three prior therapies and more than 90% with prior radiation and surgery.

- The overall response rate was 36%, 34% had stable disease and 3% had a mixed response.
- 30% bone marrow response rate for patients with bone marrow disease (69 patients with complete or partial responses).
- The response rate was better for the higher MIBG dose, 37% at 18 mCi/kg versus 25% at 12 mCi/kg.
- At 1 year, the event-free survival (EFS) was 18% (EFS is the amount of time after treatment that a patient remains without the disease returning/progressing). Overall survival (OS) at 2 years was 29% (OS is the percentage/number of patients alive in a study at the time of reporting, either with or without active tumor). EFS was longer for patients who had a complete response (CR) or partial response (PR) to the therapy.
- EFS was better for older patients (possibly due to smaller number of patients with MYCN amplified disease) and for patients who had 2 or less prior treatment regimens. Age was also closely associated with time from diagnosis.
- Side-effects included diminished platelet production, neutropenia, infections, and febrile neutropenia. 4 patients developed secondary cancers - myelodysplastic syndrome (MDS) and Acute Myeloid Leukemia (AML).

As a monotherapy, ^{131}I-MIBG has one of the highest disease response rates, with manageable side-effects. At this time, the maximum tolerated dose for ^{131}I-MIBG therapy as a singular agent is limited mainly by the impact on the bone marrow and radioactivity exposure issues.[12]

The most common immediate side-effects of MIBG therapy are:

1. Nausea and vomiting (specifically at the time of the MIBG infusion).
2. Parotid gland swelling and pain (in the first 24-48 hours post infusion), often described as jaw pain and can lead to dry mouth.
3. Elevated liver function tests.[13]

The most common medium-term side effects of MIBG therapy are:

1. Suppressed bone marrow production, specifically platelet production.
2. Neutropenia (low number of infection fighting white blood cells).
3. Infections.

The long-term side-effects of MIBG therapy are:[14]

1. Potential development of hypothyroidism which requires thyroid replacement therapy.

2. Possible increased risk of contracting a secondary cancer, most specifically MDS and AML.

The late-effects of MIBG therapy make it especially important for patients who have experienced this treatment to be in a long-term follow-up program.[15]

A retrospective research study suggests that ^{131}I-MIBG therapy is an effective treatment option for adolescent and adult neuroblastoma patients with an overall response rate of 46% and an average post-treatment survival time of 23 months. Patients 18 years of age or older had higher response rates which is attributed to the indolent disease characteristics of older patients.[16] A different research study[17] examined the use of a double dose of ^{131}I-MIBG (monotherapy) given 14 days apart followed by stem-cell rescue. The cumulative dosing for the two infusions was 36 mCi/kg. It was found that two sequential doses of ^{131}I-MIBG is tolerable; however, in this study, its ability to address bone marrow disease was limited, with only 2/13 patients with bone marrow disease clearing tumor from the bone marrow. This finding supported further trials which added other agents to MIBG that potentially could improve bone marrow response.

Current MIBG Therapy Techniques for Relapsed and Refractory Disease

The next stage in clinical trials for MIBG therapy has been the introduction of different chemotherapy combinations before, after or during the treatment with ^{131}I-MIBG. The following reviews a few of these research studies:

1. ^{131}I-MIBG with topotecan.
   - Topotecan has single-agent activity against neuroblastoma and is also known to act as a radiosensitizer (an agent that makes disease more susceptible to radiation therapy). A phase 1 study examined how the precise absorbed radiation dose can be measured from two ^{131}I-MIBG treatments and to determine if it is possible to add topotecan to the treatment regimen.[18] A previous study (an in vitro/in vivo study using mice)[19] had determined that the simultaneous administration of topotecan was more effective than the administration of topotecan 24 hours before or after ^{131}I-MIBG. Eight patients received the treatment with no unanticipated side-effects. The study helped to identify a possible system to measure how the dose of the radiation can be measured throughout the body (whole-body dosimetry).

2. ^{131}I-MIBG with vorinostat.
   - Laboratory testing[20] led to the development of a phase 1 trial to determine the appropriate dosing of vorinostat in the treatment of solid tumor cancers.[21] In a further study, vorinostat was used to sensitize neuroblastoma cells to radiation by increasing the uptake of MIBG into the cancer cells, and resulted in reduced tumor growth (laboratory and mouse models).[22]
   - A phase 1 New Approaches to Neuroblastoma Therapy (NANT) trial studied the maximum tolerated dose (MTD)[23] when using vorinostat and ^{131}I-MIBG together.[24] Vorinostat was given orally once a day on days 1-14 and ^{131}I-MIBG (dosing levels of 8-18 mCi/kg) was administered on day 3, with stem cell rescue on day 17. Side-effects included neutropenia and low potassium levels (hypokalemia). In long-term follow-up, 2 patients developed MDS/AML.
   - Overall response of 3/25 (12%, CR and PR), MIBG response of 7/25 (28%), CT/MRI response 4/18 (22%, soft tissue) and Bone Marrow response 2/16 (13%). The response was lower than MIBG as a single-agent in this phase 1 study in which most patients received less than the maximum dose of ^{131}I-MIBG.

3. ^{131}I-MIBG with vincristine and irinotecan for relapsed and refractory disease.
   - A phase 1 study showed that vincristine and irinotecan could be given with ^{131}I-MIBG at the (usual) dose of 18mCi/kg. As a phase 1 study, the primary goal was to determine dosing and side-effects; however, it did report a 25% overall response rate. 25% of the first 24 patients experienced diarrhea (grade 3) from the irinotecan.[25]
   - A phase 1/2 study was then designed to use a higher-dose but shorter course of irinotecan to address the side-effect profile of irinotecan and determine the best timing for drug delivery to maximize the radiosensitizing effects of irinotecan with ^{131}I-MIBG.[26] The addition of vincristine was to act synergistically with irinotecan.
   - Cefixime or cefpodoxime antibiotics were given to help reduce the risk of diarrhea. If eligible, patients could receive a second course of ^{131}I-MIBG at least 42 days after the first infusion. Most common side-effects were nausea, vomiting, diarrhea (but lower rates were seen in severe diarrhea than the phase 1 trial), neutropenia, and low platelets (thrombocytopenia).
   - 28% (9/32 4 CR, 5PR) overall response rate was very similar to the 25% response rate in the phase 1 trial mentioned above. 15/31 (48%) for MIBG response, 3/15 (20%) for CT response (soft tissue) and 7/21 (33%) for bone marrow response (which was higher than the previous study which was 8%).

4. ^{131}I-MIBG incorporated into myeloablative (stem-cell) transplant regimen for relapsed and refractory disease.
   - ^{131}I-MIBG with carboplatin, etoposide, and melphalan (CEM) myeloablative doses[27] (with dosing determined in a pilot[28] and phase 1 study[29]). Cohort 1 consisted of patients who did not respond (NR) to induction therapy or who had progressive disease (PD) at some point after diagnosis. Cohort 2 consisted of patients who had a partial response (PR) at the end of induction (and had to include at least 4 cycles of induction therapy but not include a phase 3 COG protocol) and were considered to have a PR at the time of enrollment onto the study. Day -21 MIBG therapy, days -7 to -5 CEM, day -4, CE, days -3 to -1 rest, day 0 stem-cell infusion, day +42 radiation and day +60 response evaluation. Timing of the MIBG was done so that the bone marrow suppression effects of both the MIBG and the CEM chemotherapies would occur at the same time. MIBG dosing was 8 or 12 mCi/kg based on the patient's baseline kidney function (GFR).
     a. Cohort 1: 4/41 (10%, CR and PR). Site specific responses scored by MIBG scan (CR/PR) in 13/41 (33%), 26/41 (65%) had SD, and 1/41 (3%) had PD. 2/21 (10%) patients noted responses of soft tissue disease, measured by CT/MRI and SD in 14/21 (81%) of patients, and 2 (10%) with PD. Bone marrow responses included 4/25 (16%) with CR, 19/25 (76%) SD, and 2/25 with PD. 3-year EFS was 20% +/- 7%. 3-year OS was 62% +/- 8%.
     b. Cohort 2: 3/8 (38%, CR and PR). MIBG scan response in 5/8 (63%) and CT/MRI response in 1/3 (33%) for patients with soft tissue disease. 0/2 with bone marrow response.

The 3-year EFS and OS was 38% +/- 17% and the 3 year OS was 75% +/- 15%.

c. 48/50 required radio-protective isolation for seven days or less and 2 patients required radio-protective isolation for eight and nine days. The median of 10 days for engraftment for neutrophils and 15 days for platelets after stem-cell infusion. Two patients died from hepatic sinusoidal obstruction syndrome (SOS, otherwise known as VOD, associated with the whole body radiation and the protocol was amended, with 6 patients total experiencing SOS). 35 (70%) of the patients developed febrile neutropenia which were due to bacterial infections in 14 patients. No fungal infections were noted.

d. At the time of the publication, 28/50 patients had died: 2 from SOS, 2 from multi-organ failure due to subsequent therapy, 23 from progressive disease, and 1 patient who developed secondary AML 3+ years after completing this protocol (died from progressive NB, AML in remission). The addition of MIBG did not impact bone marrow or organ toxicity. Low overall response rates occurred in patients with relapsed or refractory disease and higher rates of response were observed in patients who entered the study with a partial response to induction therapy (this was a small cohort and difficult to make any solid conclusions).

Other research studies have involved the combination of ^{131}I-MIBG with cisplatin[30], melphalan[31], BuMel[32], hyperbaric oxygen therapy[33], and others.

Current MIBG Trials of Note:

NCT02035137: ^{131}I-MIBG Alone vs ^{131}I-MIBG with Vincristine and Irinotecan versus ^{131}I-MIBG with Vorinostat (https://clinicaltrials.gov/ct2/show/NCT02035137)
This is a NANT phase 2 clinical trial with relapsed and refractory patients being randomized into one of three arms of the study:

1. ^{131}I-MIBG only (control arm of the study at 18 mCi/kg dose)
2. ^{131}I-MIBG (18 mCi/kg dose) with vincristine and irinotecan given by intravenous (IV) with cefixime (or equivalent) antibiotic for diarrhea side-effects of irinotecan.
3. ^{131}I-MIBG (18 mCi/kg dose) with vorinostat (oral).

Since the prior studies of ^{131}I-MIBG with irinotecan or vorinostat were smaller studies and used a range of ^{131}I-MIBG doses, the goal of this study is to determine whether the addition of these potential "helper" medications increases the response rate to ^{131}I-MIBG compared to ^{131}I-MIBG when given on its own. This trial was recently updated with two important changes:

1. Patients with prior ^{131}I-MIBG therapy will be considered for this trial.
2. The stem-cell rescue can now be done at a hospital that is not affiliated with NANT so that patients and families can return home as soon as possible once they are cleared to leave radio-protective isolation.

Other ^{131}I-MIBG therapy trials include:

1. Examination of the treatment as a monotherapy. Some of these trials are single institution trials where the clinical trial will only be available at that one hospital. However, consortium trials such as those offered by NANT will be available at multiple institutions. https://clinicaltrials.gov/ct2/results?term=mibg+and+neuroblastoma&recr=Open
2. Understanding imaging and full-body dosing (dosimetry). NCT01583842 https://clinicaltrials.gov/ct2/show/NCT01583842

Movement of ^{131}I-MIBG into Frontline Treatment:

The movement of ^{131}I-MIBG therapy into frontline treatment for patients with newly diagnosed neuroblastoma is an emerging field of study. The following are some examples of the work that has been done and what is in progress:

1. **Italy**: 13 patients with high-risk neuroblastoma were treated with induction chemotherapies (cisplatin, cyclophosphamide, etoposide, vincristine, and doxorubicin) and ^{131}I-MIBG therapy (doses as high as 16.6 mCi/kg). Side-effects were similar to chemotherapy alone. There were 2 complete responses, 6 very good partial responses, 4 partial responses, and 1 mixed response.[34]

2. **Netherlands**: In one study, patients received 2 courses of MIBG therapy, followed by surgery (and if surgery was not feasible, patients received up to two more course of MIBG therapy), and then continued with conventional chemotherapy. The objective response rate for this protocol was 66%. 58% of patients had bone marrow clear after two cycles of ^{131}I-MIBG. 17/41 patients went on to receive high-dose chemotherapy with stem cell rescue.[35] Promising results were also seen in a previous study where doses of 30-40 mCi/kg were used for ^{131}I-MIBG as the first line of treatment during induction for newly diagnosed high-risk neuroblastoma patients.[36]

3. **Netherlands**: A recently published paper detailed a small study involving two successive cycles of ^{131}I-MIBG therapy, with subsequent daily 1-hour IV infusions of topotecan for 5 days.[37] The remainder of the treatment involved four cycles of VECI (vincristine, tenipocide, carboplatin, and ifosfamide), surgery, myeloablative therapy with carboplatin and melphalan followed by stem-cell transplant and then 13-*cis*RA (Accutane). After two courses of 131I-MIBG therapy, the overall objective response rate was 9/16 (57%) with a response rate of 94% for the primary tumor and 43% for the bone marrow. At the end of the full treatment protocol, the overall objective response rate remained at 57%. The use of two cycles of 131I-MIBG therapy did not delay the VECI induction chemotherapy in any of the patients.

4. **Germany**: Incorporation of ^{131}I-MIBG therapy for patients who have remaining disease after induction (47 patients treated at 8.9 mCi/kg). The addition showed no survival advantage for those patients who were treated with ^{131}I-MIBG.[38] Another trial, following a similar process (111 patients treated at 12 mCi/kg) had a 3 year EFS of 49%, compared to the control group with a 3 year EFS of 33% who did not receive ^{131}I-MIBG therapy; however, the overall survival was identical between the two groups at 59%.[39] With these two trials, it is important to note that a lower dose of ^{131}I-MIBG was used other than the standard 18mCi/kg.

5. **In Progress**: (NCT01175356) Induction Therapy Including 131I-MIBG and Chemotherapy in Treating Patients with Newly Diagnosed High-Risk Neuroblastoma Undergoing Stem Cell Transplant, Radiation Therapy, and Maintenance Therapy with Isotretinoin (https://clinicaltrials.gov/ct2/show/NCT01175356) This pilot Children's Oncology Group study involves induction chemotherapy

(cyclophosphamide, topotecan, cisplatin, etoposide, vincristine, and doxorubicin), with surgical resection of the tumor (if possible), ^{131}I-MIBG therapy, busulphan and melphalan (BuMel) for autologous hematopietic stem-cell transplant, external beam radiation, and isotretinoin (Accutane). This trial is for patients who are newly diagnosed with neuroblastoma.

Possible Misconceptions about MIBG Therapy

^{131}I-MIBG therapy is a very different treatment from chemotherapy and standard external beam radiation. When families and patients are considering the MIBG therapy, there is a great deal of information to learn and understand. The following are some questions that you might have about the therapy:

1. Should MIBG therapy be kept as a treatment option if others therapies fail?

- When a patient first relapses, their bone marrow may be in the best position to face a treatment such as MIBG therapy. After relapse, as patients receive more therapy, their bone marrow will become weaker and may not be able to handle a therapy such as ^{131}I-MIBG as well. Since ^{131}I-MIBG has one of the highest response rates in patients with relapsed or refractory disease, many centers pursue ^{131}I-MIBG as part of therapy for a patient with first episode of relapse.

2. Will dealing with the side-effects of chemotherapy and MIBG therapy together be too much?

- When chemotherapy is given with ^{131}I-MIBG therapy, the chemotherapy is timed to be given in such a way that it will work together with the ^{131}I-MIBG and so that the side-effects of the two therapies will occur at the same time. Many studies have now shown that the combination of chemotherapy and ^{131}I-MIBG result in side-effects that are not very different to those experienced by one of the therapies alone. Supportive medications are given to patients to help address issues of nausea, vomiting, low counts, diarrhea, and other side-effects. As always, it is important to work carefully with your care team to ensure that side-effects are properly managed and addressed as soon as possible.

3. Are the radiation safety requirements too stringent and will this mean being separated from my child for too long?

    - The safety requirements are in place to ensure everyone's safety – the parents, family, doctors, nurses, hospital staff, and all others. To ensure that everyone is safe, patients, families and their care team must work together. It is important for patients and families to understand what is expected of them, and it is also important for doctors and nurses to understand the needs of the family as they navigate through a new treatment modality. MIBG therapy needs to be a good fit for the patient and the family. Children must be able to stay in relative isolation and although they are not alone, they will not be able to have their parents directly by their side like they may be used to having. The patient must be able to remain in the bed, in most cases a urinary catheter is placed and should not be removed, and they must also be able to take the required oral thyroid blocking medications. Parents and families must understand all of the necessary precautions due to the radioactivity, how to handle urine and stool clean-ups, and all of the safety precautions when returning home. Radiation isolation may be different at each of the MIBG treatment centres. In the United States of America, radiation safety is regulated by individual state laws and in Canada radiation safety is regulated by the Canadian Nuclear Safety Commission.

4. Why is MIBG therapy not available everywhere?

    - MIBG remains an "orphan drug" that is not yet approved for any specific indication in cancer. It is therefore only available to be given as part of an approved investigational clinical trial. More centers are developing MIBG therapy programs; however these require specialized rooms and specialized staff to manage patients safely, which has limited its universal availability.

Conclusions:

MIBG therapy for children with high-risk neuroblastoma is an active and well tolerated therapy. There is still much to learn about MIBG therapy and there are many areas of potential future study. These may involve:

1. Development of a better understanding of moving ^{131}I-MIBG into frontline treatment for newly diagnosed neuroblastoma patients. Establishing the best timing on when to give ^{131}I-MIBG and whether it should occur in multiple doses.
2. Understanding the effective management of short and long-term side-effects, specifically in the area of thyroid protection to reduce the risk of future thyroid dysfunction in patients.
3. Development of useful combinations of ^{131}I-MIBG and chemotherapy that address all sites of tumor, specifically in the bone marrow.
4. Establishing a better understanding of late-effects for high-risk patients with differing genetic mutations and differing age groups.
5. The possible combination of MIBG therapy with a biological therapy (immunotherapy).
6. Examination of other methods of MIBG uptake, specifically in patients who do not have MIBG avid disease (or adequate norepinephrine transport, NET, protein expression).[40]
7. Understanding measuring the dosing of 131I-MIBG at various sites of disease in the body to understand the uptake of MIBG (e.g., in soft-tissue, bone marrow, etc.).

Since the 1980s, MIBG therapy has evolved to become an important treatment regimen for high-risk neuroblastoma. If you are considering this therapy, please speak with your medical care team, or contact the research consortium running the trial (e.g., NANT, COG).

For more information from the parent perspective on MIBG therapy, please see the chapter in the Children's Neuroblastoma Cancer Foundation Handbook [LINK].

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