mIBG-based theranostics

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theranosis / theranostics (theragnostic)

**Indirect methods**

1. Sister ‘imaging’ isotope
   - I-131 ↔ I-123 (SPECT)
   - I-131 ↔ I-124 (PET)
   - Y-90 ↔ Y-86 (PET)

2. Another ‘imaging’ isotope
   - On same molecule
     - Y-90 ↔ In-111 (SPECT)

   + Good image quality
   - More expensive
   - Distribution may be different
   - Half-life need to match

**Direct methods**

3. Additional gamma or positron of therapeutic isotope
   - Lu-177 → 208 keV (SPECT)
   - I-131 → 364 keV (SPECT)

4. Secondary Brehmstrahlung photons generated by β particle
   - Y-90

   + Therapeutic Distribution
   - Image quality

Li, Theranostics, accepted for pub. 2017
### mIBG-theranostics family

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-131 mIBG</td>
<td>high e gamma, beta-</td>
</tr>
<tr>
<td>I-123 mIBG</td>
<td>low e gamma, Auger e0</td>
</tr>
<tr>
<td>I-125 mIBG</td>
<td>very low e gamma, Auger e0</td>
</tr>
<tr>
<td>I-124 mIBG</td>
<td>high e gamma, beta+</td>
</tr>
<tr>
<td>At-211 mABG</td>
<td>alpha</td>
</tr>
<tr>
<td>F-18 MFBG</td>
<td>beta+</td>
</tr>
</tbody>
</table>
mIBG therapy milestones (neuroblastoma)

First publication in Pubmed:
O.Hartmann & JD.Lumbroso, ProgClinBiolRes 1988

I131-mIBG dosimetry: M.Fielding & G.Flux, EJNM1991


First line therapy: C.Hoefnagel & J.De Kraker, EurJCancer1995

Treatment with I125-mIBG: JC.Sisson & B.Shapiro, AmJClinOncol 1996

Phase 1 dose escalation study: KK. Matthay, JClinOncol 1998

Megatherapy (+CT+ABMT): A.Garavente & B. De Benardi, BMT2001

Split double dose therapy: MN.Gaze & GD.Flux, CB&R2007

I131-mIBG / Lu177-Octate: MN.Gaze, 2017
mIBG therapy milestones (neuroblastoma)

Radiosensitizers:
mIBG therapy: indications

1. Inoperable **phaeochromocytoma**
2. Inoperable **paraganglioma**
3. Inoperable carcinoid tumour
4. Stage III or IV **neuroblastoma**
5. Metastatic or recurrent medullary thyroid cancer

www.eanm.org/publications/guidlines
mIBG therapy in neuroblastoma:
← one of the most effective single-agents !!

1. Induction therapy (upfront)
   Kraal, Pediatr Blood Cancer 2015 (Topotecan RS)

2. Consolidation therapy
   Yanik, Biol Blood Marrow Transpl 2015 (CT, ABMT)

3. Relapsed/refractory therapy
   Lee, Pediatr Blood Cancer 2017 (BMT)
   Dubois, Clin Cancer Res 2015 (Vorinostat RS)

4. Localized unresectable NB

5. Palliative therapy!
mIBG therapy in metastatic pheochromocytoma/paraganglioma
← first-line therapy !!

1. Upfront therapy in metastatic malignant pheochromocytoma
2. (Consolidation therapy)
3. Relapsed/refractory therapy
4. (Localized unresected (malignant) pheochromocytoma)
5. Palliative therapy
mIBG therapy in metastatic pheochromocytoma/paraganglioma

first-line therapy !!

Shilkrut: n=10 145+-/5mCi 11,6 +/1,6GBq 0%CR30%PR50%50%SDHR50%SR
Am J Clin Oncol 2010

Gonias: n=55 m12mCi/kg 492-3190mCi+BM 22+35CR+PR5Y64%GR3/4N87%T83%
J Clin Oncol 2009

Krempf: n=15 250mCi-3m. 11,1-85,9GBq 0%CR33%PR(29-54m.)HR50%(5-48m.)
J Clin Endocrinol Metab 1991
mIBG therapy: contra-indications

**Absolute:**
1. Pregnancy; breast feeding
2. Life expectancy less than 3 months, unless in case of intractable bone pain
3. Renal insufficiency, requiring dialysis on short term → Acute renal failure

**Relative:**
1. Unacceptable medical risk for isolation, unmanageable urinary incontinence
2. Rapidly deteriorating renal function—glomerular filtration rate less than 30 ml/min → Hemodialysis: Rahimi, Clin Nucl Med 2017
3. Progressive haematological and/or renal toxicity because of prior treatment
4. Myelosuppression:
   → Total white cell count less than 3.0×10⁹/l; Platelets less than 100×10⁹/l → PBSC, ABMT

www.eanm.org/publications/guidlines
mIBG therapy: preparation

1. Interfering medication
2. Thyroid blockade
3. mIBG dosimetry therapy planning
### mIBG therapy preparation: Interfering medication

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug names, (indications)</th>
<th>Suspension (pharm. half-life!)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CNS Stimulants</strong></td>
<td>Cocaine / amphetamines (obesity!) /caffeine (power drinks!)</td>
<td>24 / 48 / 24 hours</td>
</tr>
<tr>
<td><strong>Anti-depressants</strong></td>
<td>Tricyclic / monoamine uptake inhibitors</td>
<td>48 hours**</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td>“Major tranquilizers”</td>
<td>24-72 hours (<strong>; depot: 1 month)</strong></td>
</tr>
<tr>
<td><strong>Sedating antihistamines</strong></td>
<td>Promethazine</td>
<td>24 hours</td>
</tr>
<tr>
<td><strong>Antihypertensiva</strong></td>
<td>Adrenergic neurone blockers / Alfa blockers (prostate hypertrophy!) / Calcium channel</td>
<td>48 hours / 72 hours (<strong>2-3 weeks)</strong> / 24-48 hours / 48 hours</td>
</tr>
<tr>
<td><strong>Amiodarone</strong></td>
<td>?</td>
<td>-</td>
</tr>
<tr>
<td><strong>Sympatico-mimetics</strong></td>
<td>(COPD / inotropics / nasal / eye-glaucoma)</td>
<td>24 hours / 24 hours / 24-48 hours / 48 hours</td>
</tr>
<tr>
<td><strong>Other adrenoceptor stimulants</strong></td>
<td>Orciprenaline</td>
<td>24 hours</td>
</tr>
<tr>
<td><strong>Opioid analgesics</strong></td>
<td>Tramadol, ..</td>
<td>24 hours</td>
</tr>
<tr>
<td><strong>Herbal therapies</strong></td>
<td>Ma huang, St.John’s wort, yohimbine</td>
<td>****</td>
</tr>
</tbody>
</table>

*:preferably 1 week for all potential interacting medicines (although some longer: **); ***:labetolol: 72 hours; phenoxybenzamine: IV>PO, 15 days.; ****:may consider avoiding all herbal therapy unless the mechanism of action is well established
**mIBG therapy preparation: thyroid blockade**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Adults (15–50 kg)</th>
<th>Children (5–15 kg)</th>
<th>Children (&lt;5 kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsules mg/daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Potassium iodate</em></td>
<td>170</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td><em>Potassium iodide (KI)</em></td>
<td>130</td>
<td>65</td>
<td>32</td>
</tr>
<tr>
<td>Lugol solution 1%</td>
<td>1 drop/kg per day</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Potassium perchlorate</em></td>
<td>400</td>
<td>300</td>
<td>200</td>
</tr>
</tbody>
</table>

Lugol solution 1% 1 drop/kg per day with a maximum of 40 (20 drops twice daily).
mIBG therapy preparation: thyroid blockade


- Overall 10-15% visible thyroid
- Hypothyroidism rarely reported (underestimated, subclinical, general condition)
- Probably cumulative effect with multiple doses; may take several years.
- Check formulation & compliance
- Perform thyroid dosimetry
- Check TSH in follow-up
- **Children, long survival**: consider block/replacement therapy (antithyroidea+T4)
mIBG therapy preparation: *pre-therapy* dosimetry planning

**Standard methodology UZ Ghent:**
Preparation equal to I131-MIBG therapy (intake, medications)
Transmission scan for body contouring and attenuation correction
I-123 whole-body scanning at 10 min., 5-6 hr, 20-24 hr, 48-72 hr (74 MBq/5 MBq/kg)/LEHR
Each with IV blood sample for radioactivity counting of plasma
Reference standard in the field (legs): 0,1 mCi WB scan speed 8 cm/min
Urination after the first scan, before next scans! Count residual activity in the syringe!
Calculate counts->activity->residence time->radiation dose
Compute whole body radiation dose in Gy (OLINDA)

**Maximum administrable activity** 200 (300) mCi / 7,4 (11,1) MBq ➔ **Maximum** WB dose 2 Gy
Validation: correlation I123 WB pre-therapy dosimetry with post-therapy I131: 0,93

*Monsieurs, EJNM 2002*
mIBG therapy preparation: *pre-therapy* dosimetry planning

**MIBG Dosimetry references**

George, *Flux* - Nucl Med Comm 2016
Minguez, *Flux* – Med Phys 2015
Ramonaheng – Phys Med 2016
Chittenden, *Flux* – CB&R 2007
Buckley, *Flux* – CB&R 2007
mIBG therapy: infusion

Product defrosted after patient admitted

High specific activity carrier-free MIBG: Chin, JNM 2014

1 liter glu 5% IV / 24 hours during the first 24 hours
Double check stable IV line !!

EANM: “Temporary nausea and vomiting may occur during the first 2 days after administration”
R/ Ondansetron (5-HT3 antagonist) 1 amp IV 30-60 minutes before infusion; ½ ampul if necessary < 24 hours
Alternatives per os: domperidon, alizapride
Beware: extended QT-interval and risk on torsade de pointes; risk factors: combined affecting drugs; age > 65yr., choric heart conditions, females, electrolyte disorders;
Extra fluids per os reduce radiation effects; light meals first day.
mIBG therapy: infusion

Infusion speed: 1-2 hours regular (*mIBG not very stable after defrosting-max 4 hours at room temperature*)

EANM: “Rarely, deterioration of renal function is observed in patients whose kidneys have been compromised by intensive pretreatment with cisplatin and ifosfamide.”
mIBG therapy: early side effects

EANM: “Rarely, in adults with phaeochromocytoma or paraganglioma, and children with neuroblastoma, hypertensive crises may be evoked by release of catecholamines, requiring alpha blockade.”

Neuroblastoma: 51.3% at least one episode of elevated systolic BP, <<48 hours, 2.8% required nifedipine (sublingual!).
Feochromocytoma: Higher incidences.
- Premedication with ant-hypertensiva may control blood pressure before, during and after mIBG
- However, many of these drugs interfere with mIBG uptake in the tumors

Depending on risk: 1. therapeutic administration of mIBG are conducted without changing the medication taken, although drugs could impair the efficacy of procedure (catecholamine products in blood, urine).
2. interfering drugs are interrupted as shortly as possible BUT “considerable number of such patients with catecholamine-secreting tumours are at risk to develop symptoms after withdrawal of their medication.”
3. at infusion, phenoxybenzamine, nitrendipine, and/or magnesium sulphate IV may be required, 4. a slow administration of the mIBG, which should be stopped if hypertension occurs, is recommended.
mIBG therapy: late side effects

1. Hypothyroidism (after inadequate thyroid blockade)

2. Hematotoxicity
   a. Temporary myelosuppression which typically occurs 4–6 weeks post-therapy. Haematological effects are common in children with neuroblastoma after chemotherapy (60%), predominantly as an isolated thrombocytopenia, but are less frequent in adults.

   b. 131I-mIBG therapy is associated with significantly less haematological toxicity in chemotherapy naïve patients.

   c. Persistent haematological effects (thrombocytopenia, myelosuppression) are more likely in patients who have bone marrow involvement at the time of 131I-mIBG therapy and, because of a high whole-body radiation dose, in patients with delayed renal 131I-mIBG clearance.
mIBG therapy: late side effects

Secondary malignancy

There is sparse evidence for induction of leukaemia or secondary solid tumours, but this is a rare possibility, especially in conjunction with (longstanding) chemotherapy treatment [15]

“The cumulative risk of SMN after (131)I-MIBG therapy for patients with relapsed or refractory neuroblastoma is similar to the greatest published incidence for high-risk neuroblastoma after myeloablative therapy, with no dose-dependent Increase (n=644).”

Thirteen patients were diagnosed with haematologic malignancies, including acute myelogenous leukaemia (n=7) and acute lymphoblastic leukaemia (n=2). The remaining 4 patients had myelodysplastic syndrome. Six patients were diagnosed with solid tumours, including osteosarcoma, papillary thyroid carcinoma, peritoneal mesothelioma and an inflammatory myofibroblastic tumour. One patient developed two distinct second malignancies, an undifferentiated sarcoma of the cranium and an inflammatory myofibroblastic pseudotumour of the lung (without an identifiable ALK aberration).

Huibregtse, Matthay, Eur J Cancer 2016
mIBG therapy: *per-therapy* dosimetry

Royal Marsden methodology in Neuroblastoma

Ceiing mounted NaI and Geiger counters record
Positions constant in field of view!
First measurement shortly after administration, 2 / min.
Whole-body retention curve over time
Cumulated activity whole body A by integration
Mean absorbed WB dose $D$ (Gy) = $A$ (MBq/hr) * S factor (Gy/MBq*hr)

“Tandem infusion” or “double-dose”:
$I^{131}$-MIBG 444 MBq/kg at day 0
Per-therapy dosimetry
$I^{131}$ to give a combined WB dose of 4Gy at day 14
PBSC at day 24-28

Mean adm.activity: 11089 +/- 7222 MBq -> Mean WB dose 1,79 Gy (range 0,93-3,51)->
CTCAE Tox grade 3/4neutropenia 82%; ¼ trombocytopenia 71%-> CR 8% PR 50% SD 29%

George, Flux, Nucl Med Comm 2016
Royal Marsden methodology in Neuroblastoma

Buckley, Chittenden, Flux, J NuclMed 2009
131I-MIBG activity per kilogram correlates with WBD.

Activity per kilogram will predict WBD in most patients.

Within the range of activities prescribed, there was no correlation between WBD and either response or toxicity.

Future studies should evaluate tumor dosimetry, rather than just WBD, as a tool for predicting response following therapy with 131I-MIBG.

(Response but also progression-free interval and survival should be reported in these studies)

Trieu, Matthay, 2016 N=213R
mIBG-theranostics family

- $^{131}$I-mIBG: high e gamma, beta–
- $^{123}$I-mIBG: low e gamma, Auger e0
- $^{125}$I-mIBG: very low e gamma, Auger e0
- $^{124}$I-mIBG: high e gamma, beta+
- At-211 mABG: alpha
- F-18 MFBG: beta+
mIBG-theranostics

Johnson, Pediatr Blood Cancer, 2011:
*Early second (131) I-MIBG safely reduces disease burden in patients with relapsed NB
*Patients with CR by conventional (123) I-MIBG scintigraphy may have substantial disease burden, apparent on high-dose (131) I-MIBG scintigraphy.
*This supports consolidation with subsequent (131) I-MIBG therapy in cases of apparent CR.

Kayano, Nul Med Comm, 2011
*Low-dose diagnostic (123)I-MIBG whole-body scan is inferior to posttreatment (131)I-MIBG whole-body scan in malignant pheochromocytoma and paraganglioma.
*Considering the scan timing of (123)I-MIBG, 6-h images might have no superiority compared with 24-h images.
mIBG-theranosis: new approaches in mIBG therapy

PET scanning

Genetic markers and internal biodosimetry

Isotope cocktails
mIBG-theranosis: new approaches in mIBG therapy

**PET scanning:**


Biodistribution and dosimetry of 18F-Meta Fluorobenzyl Guanidine (MFBG): A first-in-human PET-CT imaging study of patients with neuroendocrine malignancies.


Patient-specific dosimetry using pretherapy [124I]m-iodobenzylguanidine ([124I]mIBG) dynamic PET/CT imaging before [131I]mIBG targeted radionuclide therapy for neuroblastoma.

mIBG-theranosis: new approaches in mIBG therapy

PET scanning:

Figure: the locations of the 12 lesions considered in this study are identified in the $^{124}$I-mIBG PET/CT images of the clinical case at 115-hr after injection.

Huang, Mol Imag Biol 2015
mIBG-theranosis: new approaches in mIBG therapy

PET scanning

Genetic markers and internal biodosimetry

Isotope cocktails
mIBG-theranosis: new approaches in mIBG therapy

Genetic markers and internal biodosimetry

Edmondson DA¹, Karski EE², Kohlgruber A³, Koneru H³, Matthay KK², Allen S², Hartmann CL³, Peterson LE⁴, DuBois SG², Coleman MA³,⁵

Transcript Analysis for Internal Biodosimetry Using Peripheral Blood from Neuroblastoma Patients Treated with (131)I-mIBG, a Targeted Radionuclide. 

Radiat Res. 2016 Sep;186(3):235-44.
mIBG-theranosis: new approaches in mIBG therapy

Selected Transcripts of Interest

<table>
<thead>
<tr>
<th>Gene</th>
<th>Name</th>
<th>Primer no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAPDH</td>
<td>Glyceraldehyde 3-phosphate dehydrogenase</td>
<td>H202758991_g1</td>
</tr>
<tr>
<td>CDKN1A</td>
<td>Cyclin-dependent kinase inhibitor 1A (p21)</td>
<td>Hs0035578_m1</td>
</tr>
<tr>
<td>FDXR</td>
<td>Ferrodoxin reductase</td>
<td>Hs00244586_m1</td>
</tr>
<tr>
<td>GADD45A</td>
<td>Growth arrest and DNA-damage-inducible alpha</td>
<td>Hs00169255_m1</td>
</tr>
<tr>
<td>DDB2</td>
<td>Damage-specific DNA binding protein 2 (XPE)</td>
<td>Hs03044953_m1</td>
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<tr>
<td>XPC</td>
<td>Xeroderma pigmentosum, complementation group C</td>
<td>Hs00190295_m1</td>
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<td>MDM2</td>
<td>E3 ubiquitin protein ligase</td>
<td>Hs00234753_m1</td>
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<tr>
<td>BCL2</td>
<td>B-cell CLL/lymphoma 2</td>
<td>Hs99999018_m1</td>
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<td>BCLXL</td>
<td>BCL2-like 1</td>
<td>Hs00236329_m1</td>
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<td>BAX</td>
<td>BCL2-associated X protein</td>
<td>Hs99990001_m1</td>
</tr>
<tr>
<td>STAT5B</td>
<td>Signal transducer and activator of transcription 5B</td>
<td>Hs00273500_m1</td>
</tr>
</tbody>
</table>

Genetic markers and internal biodosimetry

“Transcripts, which have been previously identified as biomarkers of external exposure in ex vivo whole blood and in vivo radiotherapy patients, are also good early indicators of internal exposure”
mIBG-theranosis: new approaches in mIBG therapy

PET scanning

Genetic markers and internal biodosimetry

Isotope/RN cocktails
mIBG-theranosis: relation to somatostatin theranostics
**mIBG-theranosis: take home messages**

* mIBG therapy is an effective therapy for metastatic NB and PHEO/PG
* side-effects are dose-dependant, but so are response/PFS
* mIBG has very powerful palliative effects and can then be moderately dosed
* in possible responding cases consider referral to specialized center and administration of big dose with bone marrow support
* diagnostic I123-mIBG as a theranostic agent underestimates tumor burden
* tandem dosing and radiosensitization have become important concepts from the experience of mIBG therapy
* further innovations include the use of PET scanning, internal dosimetry and isotope/RN cocktails.
mIBG therapy:

*Cardiac uptake on a mIBG posttherapy scan signifies:*
A. Cardiac tumoral activity
B. Heart failure
C. Catecholamine secretion
D. Sympathic dysfunction

+- : ?