Clinical PET/CT Evaluation of Patients with Neuroendocrine Cancer: Experience with Expanded Access IND Production and Use of $^{68}$Ga-DOTA-NOC

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OBJECTIVE

- To provide the $^{68}$Ga-DOTA-NOC radiopharmaceutical for use in clinical PET/CT evaluation of patients with neuroendocrine tumors.

BACKGROUND

- The Expanded Access IND (Investigational New Drug exemption) can be a mechanism for providing patient access to a drug product that is not FDA-approved, but that is clinically needed in treatment of a serious disease [1].

- Gallium-68-labeled somatostatin-receptor-targeted peptides, such as $^{68}$Ga-DOTA-NOC, have found widespread clinical use in Europe for positron emission tomography (PET) detection of neuroendocrine tumors [2-5], but are not FDA-approved drug products in the USA.

- In response to a local clinical need to better define the location and extent of disease in neuroendocrine cancer patients who are candidates for multivisceral transplant [6], a method was developed for on-demand preparation of the $^{68}$Ga-DOTA-NOC peptide-chelate conjugate in a formulation suitable for intravenous administration, and an Expanded Access IND submitted to the FDA documenting the production procedure and the intended clinical use.

- The positron-emitting $^{68}$Ga$^{3+}$ (68-minute half-life) is available from a long-lived parent/daughter generator system [7], forming as the decay product of long-lived $^{68}$Ge (271-day half-life). On-demand, the short-lived $^{68}$Ga$^{3+}$ daughter is selectively eluted from the generator for use in radiopharmaceutical synthesis. Continued $^{68}$Ge decay in the generator allows re-elution to deliver clinically useful levels of $^{68}$Ga at 2-3 hour intervals.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Binding Affinity for Somatostatin Receptor Subtype (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$h$SSTR1</td>
</tr>
<tr>
<td>Octreotide $^a$</td>
<td>1140</td>
</tr>
<tr>
<td>Ga-DOTA-NOC $^b$</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>Ga-DOTA-TOC $^b$</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>Ga-DOTA-TATE $^b$</td>
<td>&gt;10,000</td>
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</table>


**MATERIALS and METHODS**

- Two Eckert & Ziegler (EZAG) IGG100 $^{68}$Ge/$^{68}$Ga generators, and two ITG Isotope Technologies Garching GmbH $^{68}$Ge/$^{68}$Ga generators, have been employed to supply $^{68}$Ga for manual synthesis of $^{68}$Ga-DOTA-NOC under Expanded Access IND #117255. The DOTA-NOC peptide conjugate was purchased from ABX GmbH as commercial cGMP-grade product packaged at 60-µg per vial.

- Synthesis employed $^{68}$Ga$^{3+}$ in either 1.5 mL 0.1M ultrapure HCl (fractionated elution of the EZAG generator), or 4.0-mL 0.05M ultrapure HCl (ITG generator, without fractionation). The eluate was buffered to pH ~4.8 by addition of ultrapure NaOAc and reacted with the DOTA-NOC conjugate (60-µg for the EZAG eluate; 30-µg for the ITG eluate) with heating for 10-minutes. The $^{68}$Ga-DOTA-NOC product was isolated by C18 solid-phase extraction (C18 SepPak® Light); washed with sterile water or saline; recovered in ethanol:saline (0.6-mL, 85:15; or 1.0-mL, 50:50); and then diluted to ≤5% ethanol with sterile saline, followed by terminal sterilizing filtration into a sterile evacuated vial.

- Pre-release product quality control procedures include: half-life measurement for confirmation of radionuclidic identity; pH measurement; ITLC assessment of radiochemical purity (quantifying ionic $^{68}$Ga and colloidal $^{68}$Ga-hydroxide impurities); endotoxin testing; and a bubble point measurement to confirm the integrity of the sterile 0.2-µm filter employed for terminal product sterilization. Retrospective analysis of each production batch includes sterility testing, and measurement of $^{68}$Ge breakthrough.
PET/CT images (Siemens mCT camera) were acquired 60-minutes following i.v. administration of the $^{68}$Ga-DOTA-NOC radiopharmaceutical. All patients provided written informed consent prior to administration of the investigational radiopharmaceutical and imaging following an IRB-approved protocol.

### Table 1. $^{68}$Ga-DOTA-NOC Dose Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EZAG Generator</th>
<th>ITG Generator</th>
<th>Aggregate Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>47</td>
<td>36</td>
<td>83</td>
</tr>
<tr>
<td>Administered Dose (mCi)</td>
<td>$4.5 \pm 0.7$</td>
<td>$5.0 \pm 0.4$</td>
<td>$4.7 \pm 0.6$</td>
</tr>
<tr>
<td>DOTA-NOC Dose (µg)</td>
<td>$43.2 \pm 5.2$</td>
<td>$23.0 \pm 5.9$</td>
<td>$34.4 \pm 11.4$</td>
</tr>
<tr>
<td>Radiochemical Purity (%)</td>
<td>$98.9 \pm 0.4$</td>
<td>$99.3 \pm 0.5$</td>
<td>$99.0 \pm 0.5$</td>
</tr>
<tr>
<td>$^{68}$Ge Breakthrough at Dose Expiration Time (%)</td>
<td>$2.8 \times 10^{-7}$</td>
<td>$1.2 \times 10^{-5}$</td>
<td>$5.3 \times 10^{-6}$</td>
</tr>
<tr>
<td>Synthesis Time, Elution-to-Dose Release (minutes)</td>
<td>$46 \pm 5$</td>
<td>(median 49)</td>
<td>(median 46)</td>
</tr>
</tbody>
</table>

**RESULTS**

- Table 1 summarizes our radiopharmaceutical production experience for the 83 patient doses of $^{68}$Ga-DOTA-NOC prepared in the first 2-years of Physician-Sponsored Expanded Access IND #117,255. Product radiochemical purity was consistently high, averaging $99.0 \pm 0.5\%$.

- The level of DOTA-NOC in the administered doses (Table 1) was always in keeping with the *European Association of Nuclear Medicine Procedure Guidelines* recommendation of $\leq 50$ µg [2]. The ITG generator eluate has very low trace metals contamination, allowing reliable product synthesis with a lower mass of the DOTA-NOC peptide-conjugate (30-µg vs. 60-µg).

- $^{68}$Ge breakthrough in the $^{68}$Ga-DOTA-NOC radiopharmaceutical (Table 1) was always far below the specified 0.001% upper limit, regardless of generator manufacturer. Consistent with the manufacturers’ generator specifications, $^{68}$Ge breakthrough was higher with the ITG generator.

- Total synthesis time, from generator elution to post-QC release of final product, averaged $47 \pm 5$ minutes. Endotoxin testing was the rate-limiting QC test in progression to final dose release. The slightly longer production time with the ITG generator (Table 1) results from procedural modifications to reduce worker radiation exposure.

- $^{68}$Ga-DOTA-NOC has consistently delivered high quality PET images (Figures 1 and 2) that have significantly impacted clinical care decisions with information not available by conventional imaging. In approximately one-half the patients being screened for multi visceral transplant, $^{68}$Ga-DOTA-NOC imaging has revealed previously unknown disease in locations that preclude transplant.
Figure 1. Images of a carcinoid tumor patient obtained with both $^{68}$Ga-DOTA-NOC and $^{111}$In-Octreoscan, the only FDA-approved agent for somatostatin-receptor-targeted neuroendocrine tumor imaging. In contrast to the $^{111}$In image, which appears normal, the $^{68}$Ga image reveals multiple metastatic lesions in the liver. (The pituitary also expresses somatostatin receptors and is visualized in the $^{68}$Ga PET image, along with normal uptake in the spleen, kidneys, and bladder.) The $^{68}$Ga PET scan was performed because the patient’s symptoms were inconsistent with the $^{111}$In-Octreoscan findings.
Figure 2. Whole-body $^{68}\text{Ga}$-DOTA-NOC PET images obtained to define extent of disease in two patients being considered for transplant. Images of the patient on the left show extensive $^{68}\text{Ga}$-DOTA-NOC uptake in metastatic lesions throughout the body. Images from the patient on the right also show multiple sites of metastatic disease, but these are confined to the liver and abdominal cavity. Following evaluation with $^{68}\text{Ga}$-DOTA-NOC PET, only the patient on the right remained a candidate for treatment by multi-visceral transplant.
CONCLUSIONS

• The manual $^{68}$Ga-DOTA-NOC synthesis methods have been reliable and robust in radiopharmaceutical production for clinical use.

• PET/CT with $^{68}$Ga-DOTA-NOC has often provided unique clinical information, advancing medical care for neuroendocrine cancer patients through improved definition of the location and extent of disease.

• The Expanded Access IND has provided a valuable regulatory pathway for supplying this investigational drug, which is filling a patient care need, but would otherwise be unavailable for clinical use in the United States.

ACKNOWLEDGEMENT

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REFERENCES


Patient Eligibility and Scheduling Forms for $^{68}$Ga-DOTA-NOC PET/CT at Indiana University are available at:

http://imaging.medicine.iu.edu/research/office-for-research-imaging/office-for-research-imaging/forms-and-resources/expanded-access-acetate-and-ga-dota-noc/

For questions about patient eligibility, enrollment, or scheduling, please contact: radyco@iupui.edu

General information on PET/CT imaging in neuroendocrine cancer is available at the website of the Society of Nuclear Medicine and Molecular Imaging:

*Neuroendocrine Tumors and Molecular Imaging – Factsheet*  
(http://snmmi.files.cms-plus.com/docs/fact_sheets/NET_factsheet.pdf)