Managing a High-Specific-Activity Iobenguane Therapy Clinic: From Operations to Reimbursement

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Metaiodobenzylguanidine (MIBG, iobenguane) is a guanethidine analog that targets the norepinephrine transporter and, when radiolabeled with the β-emitter ^{131}I, has been used with varying protocols to treat neuroendocrine tumors, including pheochromocytoma/paraganglioma (PPGL), neuroblastoma, and carcinoid, in adults and children around the globe for more than 35 y (*1*). In 2018, a high-specific-activity (HSA) formulation (Azedra; Molecular Insight Pharmaceuticals, Inc.) became the first, and is currently the only, Food and Drug Administration–approved drug to treat unresectable, locally advanced, or metastatic PPGL (*2*). Multiple clinical trials are currently investigating other applications of ^{131}I-MIBG, such as for children with metastatic neuroblastoma and in combination with PRRT for patients with carcinoid tumor (*3*,*4*). We will likely see increasing Food and Drug Administration–approved and off-label use of ^{131}I-MIBG in the coming years. This editorial will discuss the operational aspects of clinical implementation and use of HSA ^{131}I-MIBG in advanced-PPGL patients. In addition to reviewing the literature, this editorial is supported by our experience in performing over 150 PPGL treatments over the last 10 y in both the inpatient and the outpatient setting.

PRETREATMENT EVALUTION AND TREATMENT OVERVIEW

Since HSA ^{131}I-MIBG is the only Food and Drug Administration–approved treatment for advanced PPGL, all patients with advanced PPGL for whom systemic anticancer therapy is being considered should undergo diagnostic ^{123}I-MIBG imaging, and HSA ^{131}I-MIBG therapy should be considered first-line in those with ^{123}I-MIBG–avid disease. Systemic therapy is not considered in patients solely on the basis of metastatic disease but is reserved for patients with clear evidence of disease progression or who have disease symptoms not controlled by supportive treatment. For example, poorly controlled catecholamine-mediated symptoms (such as hypertension or anxiety) or disease-related pain can be an indication for therapy in the absence of objective progression.

Authorized user physicians evaluate prospective patients in the clinic to ensure they meet the criteria for treatment with ^{131}I-MIBG, to explain the treatment protocol and goals of therapy, and to engage in shared decision making regarding whether and when to move forward with treatment. Patients are counseled that therapy is intended to halt progression of their disease or decrease their symptoms, hopefully for many years, but is not a disease cure (*5*,*6*). Diagnostic ^{123}I-MIBG scintigraphy is obtained to confirm ^{123}I-MIBG–avid disease and to demonstrate the patient's baseline disease burden.

In patients pursuing ^{131}I-MIBG therapy, baseline bloodwork is obtained to confirm that certain safety metrics are met, notably that platelets are greater than 80,000/μL, absolute neutrophil count is greater than 1,200/μL, and estimated glomerular filtration rate is greater than 30. A negative pregnancy test is confirmed in women of childbearing potential, and all patients are counseled to use effective contraception during treatment and for approximately 6 mo after their final therapy. Recent baseline biochemical tumor markers (chromogranin A, catecholamines, metanephrines) and anatomic imaging are important for subsequent response assessment (noting that anatomic imaging may be unhelpful in patients with bone-dominant disease). To protect patients' thyroid function, inorganic iodine is given starting the day before and for 10 d after each treatment. A complete discussion of pretreatment patient preparation can be found in the HSA ^{131}I-MIBG prescribing information (*2*).

The recommended dosing regimen includes planar dosimetry with 3 anterior and posterior whole-body scans done over 3–5 d after intravenous administration of about 185 MBq of HSA ^{131}I-MIBG. The maximum cumulative administered activity without exceeding organ limits is calculated. For on-label indications, there is no cost for the dosimetry dose. If a site does not have the expertise or software for dosimetry, third-party services are available.

The recommended administered activity for therapy is 296 MBq/kg (8 mCi/kg) up to a maximum of 18.5 GBq (500 mCi) in each of 2 treatment cycles given at least 90 d apart. For dosimetry revealing a maximum cumulative activity of less than 37 GBq, the prescribed activity for each cycle should be decreased equally. Most patients will require inpatient therapy; however, in patients with more indolent disease, lower administered activities can be given in an outpatient setting with reported efficacy. A common approach is 74 MBq/kg (2 mCi/kg) × 4 cycles at 3-mo intervals; 7.4 GBq (200 mCi) per cycle has also been used.

Between cycles, bloodwork is obtained to ensure that the absolute values and overall trends are safe before proceeding to the next therapy. Myelosuppression, specifically thrombocytopenia, is the most common toxicity of Azedra (*5*). Recovery from nadir levels is usually seen by 4–6 wk after treatment. Febrile neutropenia, grade 4 thrombocytopenia (<25,000/μL), or neutropenia

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(<500/μL) lasting more than 1 wk should prompt a 15% reduction in prescribed activity for subsequent treatment.

Scintigraphic imaging is performed about 5–7 d after therapy (or earlier on the day of hospital discharge for inpatients) to confirm successful radiotracer tumor targeting and sometimes reveals sites of disease not well seen on the lower-dose ^{123}I-MIBG diagnostic imaging. Delayed posttreatment imaging, largely focused on anatomic imaging with CT or MRI (ideally matching baseline imaging) with ^{123}I-MIBG scintigraphy as an adjunct, is performed 3 mo or more after the completion of therapy. Response to therapy is usually best assessed with anatomic imaging, biochemical tumor markers, and patient symptoms. A follow-up visit in the nuclear medicine clinic is scheduled to discuss the posttreatment imaging results, bloodwork results, symptoms, and next steps. Frequently, the authorized user physician transfers primary oversight of the patient to the patient's medical oncologist, endocrinologist, or nephrologist, depending on local expertise.

SYSTEM INFRASTRUCTURE AND INPATIENT STAY

Most HSA ^{131}I-MIBG administrations will require an inpatient stay for radiation isolation. Patients will be given a private hospital room that is wrapped—that is, with the floor and surfaces covered with impervious materials for easy cleaning and disposal after the patient's stay.

Rolling shields may be required to minimize radiation exposure to adjacent rooms. Depending on room size, administered activity, and adjacent room occupancy (including above and below), shielding requirements can vary greatly. Therapy is infused intravenously by a trained nuclear medicine technologist or authorized user. Many methods for infusion have been described, but a simple lead-shielded syringe pump is believed to be the most straightforward method with the least potential for contamination. The recommended infusion duration in adults is 30 min, but as pharmacologic effects from ^{131}I-MIBG have not been observed with the HSA preparation (in contrast to low-specific-activity ^{131}I-MIBG), more rapid infusions can be cautiously considered. To decrease exposure, staff should enter the patient's room no more than necessary but can attend to all of a patient's medical needs. A Geiger–Mueller counter with hand and foot monitoring attachments outside the patient room is helpful to assess for potential contamination each time a member of the staff leaves the room. Additionally, providing instant-read dosimeters to the health-care staff reassures that exposures are low and can spur immediate staffing changes in the unlikely event of higher exposures. We have found that with these measures in place, nursing care for our admitted patients is straightforward and often welcomed by the nurses, as our patients tend to be far less sick than the typical oncology inpatient.

Nausea and vomiting are almost ubiquitous with high-dose therapy, and scheduled antiemetics are recommended for all patients. Intravenous fluids are also recommended for all patients to minimize nausea and improve clearance of unbound radiotracer. Intravenous fluids are continued for as long as the patient can tolerate, limited either by patient preference or by signs or symptoms of volume overload. Since most ^{131}I-MIBG is excreted intact in the urine, bladder catheterization is recommended for young children and incontinent adults during hospitalization. Continent patients are encouraged to empty their bladder frequently to decrease bladder exposure. To reduce potential contamination, patients should sit when urinating, double flush the toilet, and carefully wash their hands.

Damaged and dying neuroendocrine cells can paroxysmally release large amounts of catecholamines, leading to blood pressure lability or a hypertensive crisis. Although most common within 2 d of treatment, lability can persist for weeks, and titration of antihypertensives may be needed (in many patients the optimal antihypertensive regimen will decrease after therapy) (*2*). Additionally, in patients with catecholamine-induced hyperglycemia, hypoglycemic drugs may require decreasing doses after therapy.

Radiation safety personnel will assess inpatients' radiation levels daily. In most of the United States, patients can be discharged when the exposure rate at 1 m from the patient is less than 70 μSv/h (7 mrem/h). The hospital stay for radiation isolation typically lasts 3–5 d after an 18.5-GBq administration but varies on the basis of multiple factors, including total administered activity, overall tumor burden, organ function, the patient's home living situation, and local regulations. Because the kinetics of MIBG are similar to those of sodium iodide, the radiation precautions and outpatient dose limits used for thyroid cancer patients treated with sodium ^{131}I can also be applied to PPGL patients treated with ^{131}I-MIBG.

MULTIDISCIPLINARY STAFF

Like other therapeutic and diagnostic nuclear medicine agents, HSA ^{131}I-MIBG must be handled and administered by a well-trained multidisciplinary staff. A licensed authorized user as defined by the U.S. Nuclear Regulatory Commission is responsible for the overall safe handling of radiopharmaceuticals, including ^{131}I-MIBG. Nuclear medicine technologists accept, store, and handle ^{131}I-MIBG according to standard Nuclear Regulatory Commission and agreement state operating procedures.

Health or medical physicists collaborate with authorized users to quantify safe levels of administered activities for each patient. Nurses, radiation safety officers, and environmental service employees work in patient-facing roles and non–patient-facing roles to ensure the safety of patients, their families, and hospital staff.

Institutions that currently administer other nuclear therapies likely have this multidisciplinary staff in place, and typically, no new resources are needed to initiate an HSA ^{131}I-MIBG therapy program. If needed, training given to nuclear medicine staff can easily be adapted to nursing and other health-care staff. Periodic in-service training programs and written standard operating procedures are recommended since PPGL patients are rare. Easy accessibility to a health physicist is recommended for any staff questions or concerns.

PURCHASING AND REIMBURSEMENT

Each HSA ^{131}I-MIBG patient will require a dosimetry dose and, usually, multiple therapy doses. The HSA ^{131}I-MIBG manufacturer provides a list of dates on which doses are available. There is no charge for the dosimetric dose for PPGL patients treated according to the approved indication, though the site will want to bill for the imaging acquisition. Billing for dosimetry calculations themselves is potentially feasible; guidelines are currently being created by an SNMMI Dosimetry Task Force and will be published separately. It can be helpful to provisionally place an order for a patient's expected treatment dose at the time that the dosimetry dose is ordered.

Most insurance providers have national coverage decisions for HSA ^{131}I-MIBG therapy; however, given the rarity of the disease, the coverage decision may not be included in individual center

contracts. Preauthorization is required. Additionally, working with a site's billing staff to create single-case agreements with the insurance provider is recommended as a best practice. Given the rarity of the disease, this process is a straightforward one with most payers. Although standard coverage policies or contracts will provide adequate reimbursement for most outpatient therapies, single-case agreements help to ensure that the full drug acquisition cost is added to the standard inpatient reimbursement.

The "Azedra Service Connection" is a manufacturer program designed to help providers order therapy and to help patients and providers navigate treatment logistics and payment. Financial assistance is available for eligible uninsured patients and may cover the entirety of the treatment costs. Because HSA ^{131}I-MIBG can be ordered at a per-millicurie cost, scaling of a prescription to a lower outpatient administered activity is easily done. The Centers for Medicare and Medicaid Services have granted a temporary new-technology add-on payment to increase reimbursement for inpatient Azedra therapy for Medicare beneficiaries. With preauthorization and single-case agreements, we have found providing this unique treatment to this ultra-orphan patient population to be economically viable.

CONCLUSION

A ^{131}I-MIBG therapy clinic is easily managed from both an operational and a financial aspect and serves an important role in the multidisciplinary care for PPGL patients and potentially other neuroendocrine tumor patient populations.

DISCLOSURE

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