Pheochromocytomas and Paragangliomas

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KEYWORDS

• Pheochromocytomas • Paragangliomas • Neuroendocrine tumors
• Extra-adrenal pheochromocytoma • Hypertension

KEY POINTS

- Suspected patients with pheochomocytoma/paraganglioma (PCC/PGL) will need to have plasma metanephrines or 24 hour urine catecholamines and metanephrines checked.
- Commonly used drugs that cause false positive results in diagnosis are tricyclic antidepressants, sympathomimetics (ephedrine, albuterol, amphetamines), -blockers, and caffeine.
- Imaging modalities for PCC/PGL includes CT scans, MRI, and PET scans. Newer DOTATATE scans have recently been found to be helpful.
- Treatment involves surgical removal of the tumor. There are limited options for those patients with metastatic disease.
- PCC/PGL is one of the most hereditary tumors. Patients diagnosed with PCC/PGL need to be evaluated for genetic testing.

INTRODUCTION

Pheochromocytomas (PCCs) are rare neuroendocrine tumors. About 80% to 85% of these cancers arise from chromaffin cells residing in the adrenal medulla. The remaining 15% to 20% of such tumors are extra-adrenal. These extra-adrenal lesions that arise from the autonomic neural ganglia are termed paraganglioma (PGL) or sometimes called extra-adrenal PCC.[1–4] Collectively, these tumors are often abbreviated as PCC/PGL (or PPGL) in the literature. The clinical symptoms of the disease are common between the adrenal and extra-adrenal forms and are determined by excess secretion of catecholamines (norepinephrine, epinephrine, and dopamine). Hypertension is a critical and often dramatic feature of PCC/PGL, and its most prevalent reported symptom

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(with a sensitivity of 80.7%).[5,6] However, given the rare occurrence of this cancer, in patients undergoing screening for hypertension, the prevalence of PCC/PGL ranges from 0.1% to 0.6%.[1,7–9] Still, patients frequently come to the attention of the endocrinologist when PCC/PGL is suspected as a secondary cause of hypertension.[10,11] This article summarizes current clinical approaches to patients with PCC/PGL.

GENETICS OF PHEOCHROMOCYTOMAS AND PARAGANGLIOMAS

PCC/PGL is one of the most hereditary tumors (reviewed in[12–14]), with germline mutations associated with PCC/PGL being present in neurofibromatosis (*NF-1*), multiple endocrine neoplasia (MEN2a and MEN2b), von Hippel–Lindau (*VHL*), and familial PGL syndromes.[3] Moreover, about 30% of the sporadic cases of PCC/PGL are found to harbor a known gene mutation. Early analysis of PCC/PGL tumors focused on the MEN2A and MEN2B syndromes. In fact, historical and genetic analysis confirmed that the first reported PCC was described in a patient with MEN2A.[15,16] Patients with MEN2A also present with medullary thyroid carcinoma and hyperparathyroidism. Similar to patients with MEN2A, patients with MEN2B syndrome develop PCC and medullary thyroid carcinoma; however, instead of hyperparathyroidism, they are burdened with neuromas (reviewed in[17]). Patients with NF-1 have also been recognized to have PCC in addition to neurofibromas.[18] Patients with VHL syndrome are known to have pancreatic cysts, PCC, angiomas, and renal cell carcinomas.[19]

Although renal cell carcinoma is caused by germline mutations in the *VHL* tumor suppressor gene, it is also found in carriers of mutations in the enzymes of the tricarboxylic acid cycle, such as succinate dehydrogenase (*SDHx*) subunit genes and fumarate hydratase (*FH*). Succinate dehydrogenase is involved in oxidative phosphorylation and the tricarboxylic acid cycle of mitochondrial complex II. SDHx gene mutations are inherited as autosomal dominant and act in a tumor suppressor-like fashion.[20,21] SDHB-associated PCC/PGL arise owing to inactivating mutations in the *SDHB* gene, located on chromosome 1p35 to 36. This syndrome is commonly caused by tumors localized to the skull base, neck, mediastinum, abdomen, pelvis, and adrenal medulla.[22,23] Patients with this mutation are at increased risk for malignant PGL as well as renal cell carcinoma and papillary thyroid cancer.[12,23,24] The other key *SDHx* mutation that can be seen in patients with hypertension is the *SDHD* mutation. This gene is located on chromosome 11q23. These tumors are mostly nonsecreting and are associated with parasympathetic PGLs at skull base and neck (head and neck PCC/PGL).[25] However, adrenal location for *SDHD*-associated tumors was also reported[26,27] Interestingly, penetrance of SDHD-associated disease is parent-of-origin dependent and the disease is only manifested when paternally inherited.[23,25]

There is now a better appreciation of how genetic testing improves outcomes in the management of PCC/PGL.[28] The study by Buffet and colleagues[28] demonstrated the critical importance of identifying the genetic cause of PCC/PGL (eg, *SDHx* or a *VHL* mutation) for the practical management, clinical outcome, and increasing survival of the patients. Knowing a patient's genetic predisposition ultimately resulted in the more systematic follow-up and an informed change in the management taking into account their increased genetic risk. A comprehensive work from The Cancer Genome Atlas Program has recognized that there are several clusters of gene mutations that cause PCC/PGL.[29] Cluster 1 is associated with a pseudohypoxia pathway. These tumors activate a gene expression program associated with hypoxic conditions even under normal oxygen pressure. Tumors from cluster 1 secrete norepinephrine or dopamine only, as they do not express the phenylethanolamine-N-methyl transferase (PNMT) enzyme. Within the adrenal gland, PNMT is present and converts

norepinephrine to epinephrine. PNMT expression is limited to the adrenal gland, brain, and organ of Zuckerkandl. Cortisol produced from the adrenal cortex stimulates PNMT activity in the adrenal medulla, which is critical for converting norepinephrine into epinephrine.[30] In contrast, PGL tumors do not express PNMT and secrete norepinephrine or dopamine. Examples of genetic mutations associated with these PGLs include *EGLN1*, *HIF2*, *SDHx*, *FH*, *MDH2*, and *VHL* (**Fig. 1**).

Cluster 2 tumors are associated with kinase signaling. Examples of such tumors include tumors harboring *RET* gene mutations (MEN2A and MEN2B syndromes), *NF-1*, and *TMEM127*. Tumors from cluster 2 secrete both epinephrine and norepinephrine as they express PNMT. Cluster 3 is associated with alteration in Wnt signaling pathway. The somatic genetic alterations that belong to this cluster are *MAML3* fusion genes, which are clinically associated with an aggressive and metastatic form of disease. The fourth cluster described by the consortium was a cortical admixture group of tumors that include tumors harboring the MYC-associated factor

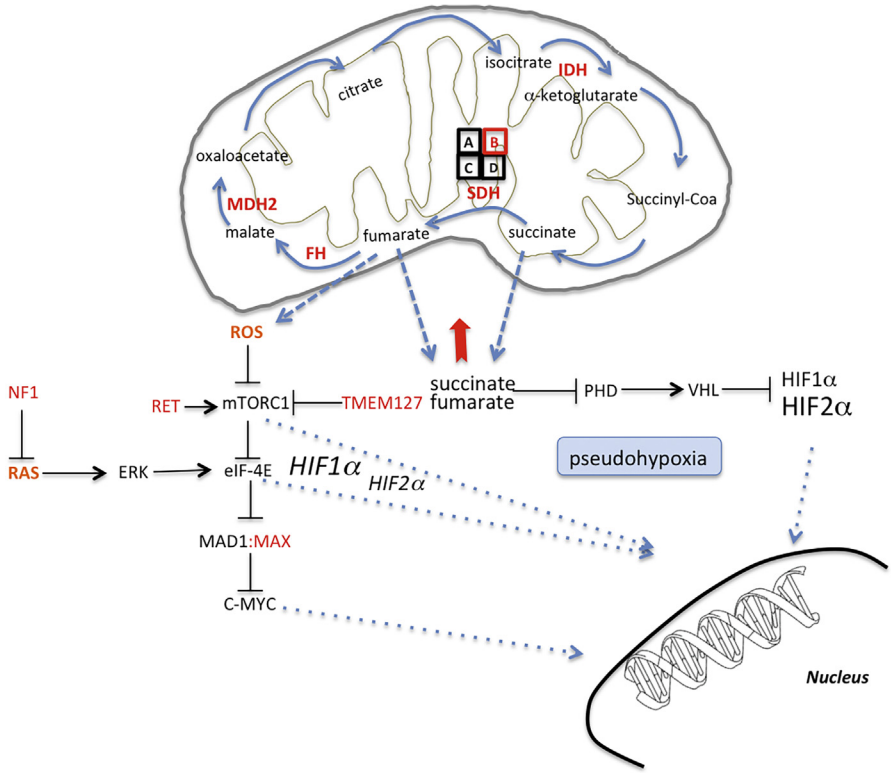

Fig. 1. The interplay between metabolic changes and tumor development in PCC/PGL. Mitochondrial genes involved in PCC/PGL development are shown in bold red; proteins involved in PCC/PGL are shown in red and pathways in orange. *c-MYC*, MYC proto-oncogene; *eIF-4E*, eukaryotic initiation factor 4E; *ERK*, extracellular signal-regulated kinase; *FH*, fumarate hydroxylase; *IDH*, isocitrate dehydrogenase; MAD1, mitotic arrest-deficient 1; MAX, Myc-associated factor X; *MDH2*, malate dehydrogenase; *mTORC1*, mammalian target of rapamycin complex 1; NF1, neurofibromin 1; *PHD*, prolyl hydroxylase domain protein; *RAS*, rat sarcoma oncogene; *RET*, rearranged during transfection proto-oncogene; *ROS*, reactive oxygen species; *SDH*, succinate dehydrogenase; *sα*, hypoxia-inducible factor alpha; *TMEM127*, trans-membrane protein 127; *VHL*, von Hippel-Lindau protein.

X gene (*MAX*) mutations. MAX-mutated tumors tend to secrete predominantly norepinephrine compared with epinephrine, likely because their PNMT level is low. Investigators have also noted that the expression level of PNMT seems to be intermediate between cluster 1 and cluster 2 in both the MAML3 fusion protein and *MAX*-associated tumors.[31] Given an ever-increasing number of gene mutations associated with PCC/PGL, genetic screening in all patients with PCC/PGL merits consideration, including patient counseling, where applicable.[2,32]

HOW PHEOCHROMOCYTOMAS AND PARAGANGLIOMAS CAUSE HYPERTENSION

Different types of PCC/PGL do not normally demonstrate distinctive patterns of hypertension, because the surge of catecholamines may be both continuous and intermittent (reviewed in[33]). These patterns lead to variations in the clinical picture where both sustained or paroxysmal hypertension could be observed.[5] Still, different catecholamines produce different vasoactive effects and in some cases these could be informative. Norepinephrine stimulation of α-receptors results in vasoconstriction, volume contraction and elevation of blood pressure (**Fig. 2**, top panel), whereas β2-receptor activation (predominantly from epinephrine) results in skeletal muscle vasodilatation and consequently postural hypotension.[34,35] Depending on the type of catecholamines produced, PCC/PGL may be grouped into noradrenergic phenotype—predominantly norepinephrine secreting (as seen in cluster 1 gene mutations) with sustained hypertension, and the adrenergic phenotype—mainly epinephrine secreting (as seen in cluster 2 gene mutations) with paroxysmal symptoms.[5] Hypertension has traditionally been thought to be uncommon in patients with purely dopamine-producing tumors. However, newer data from evaluating patients with head and neck PGLs with high 3-methoxytyramine levels (a breakdown product of dopamine) indicated that these patients have hypertension.[36,37]

CLINICAL PRESENTATION

It is widely believed that PCC/PGLs largely retain their differentiated state, endocrine function, and regulatory hormonal control. Episodic catecholamine surge by the PCC/PGL results in the classic triad of headache, sweating, and palpitations, a so-called PCC/PGL triad, also known as an attack, that may be diagnostically relevant. Although idiopathic attacks may occur in some cases, there can be multiple triggers for this characteristic disease presentation that include anesthesia, tumor manipulation, postural change, and exercise. Attacks can also be caused by different medications such as antidepressants, β-blockers, opioid analgesics, metoclopramide, and sympathomimetics.[2,5,34] Episodes of hormonal surge may also lead to a form of catecholaminergic cardiomyopathy (Takotsubo cardiomyopathy). The mechanism of this disease is not clear and both direct damage to the myocytes owing to excess catecholamines or indirect ischemic injury owing to microvascular dysfunction have been proposed.[38] A patient's first presentation could be with heart failure.[35,39] In pregnant women, the first presentation often comes with preeclampsia or eclampsia secondary to excess hormone release triggered by the pressure of enlarging gravid uterus on the tumor.[40,41]

Paroxysmal (approximately 48%) or persistent (approximately 29%) hypertension is detected in most patients with PCC/PGL and the episode can often result from mere manipulation of the tumor during surgery.[6,42] Normotension is present in about approximately 13% of patients who come to clinical attention owing to hereditary syndromes or incidental findings on imaging studies and are often asymptomatic.[10] It is important to emphasize that most patients presenting with severe hypertension or

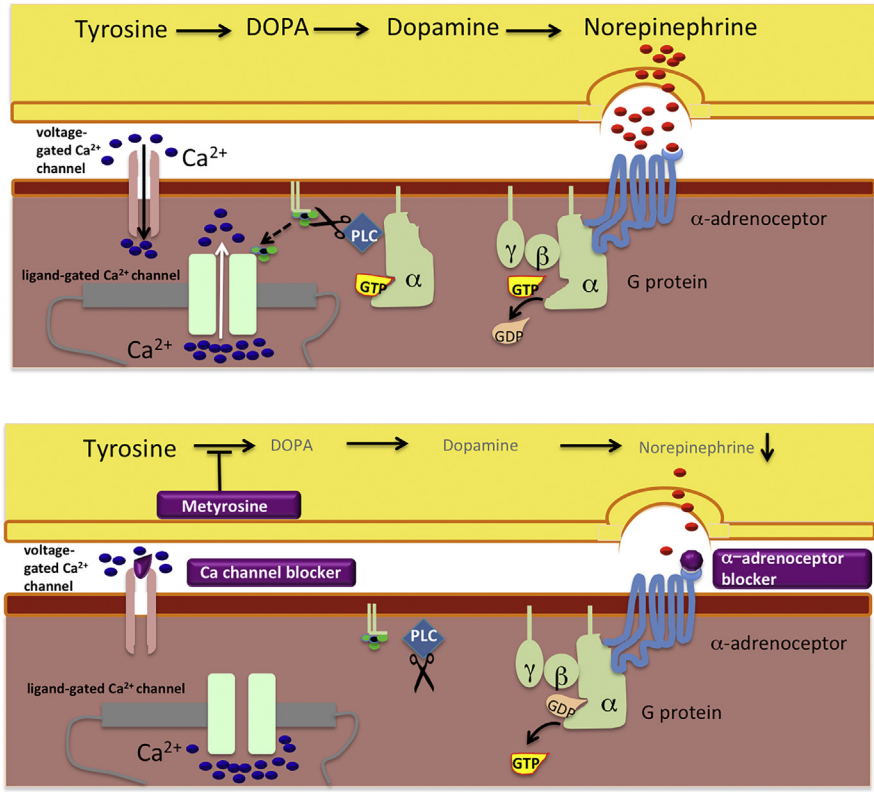

Fig. 2. (*Top*) Sympathetic-like control of BP by catecholamines in PCC/PGL. Elevated levels of catecholamines released from PCC/PGL (mostly norepinephrine) bind to α1- and α2-adrenoceptors in the smooth muscle vasculature. These adrenoceptors are coupled with G-proteins that activate phospholipase C enzyme (PLC). PLC splits a membrane-bound phospholipid phosphatidylinositol bisphosphate (PIP2) into 2 important second messenger molecules, inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 diffuses in the cytosol where it binds to its receptor, a ligand-gated Ca^{2+} channel located in the endoplasmic reticulum (or sarcoplasmic reticulum of the muscle). Stimulation of a receptor promotes the release of the Ca^{2+} into cytosol and causes the smooth muscle to contract. Another signaling molecule that results from the PIP2 hydrolyses, DAG, is lipid-soluble and remains in the membrane where it activates protein kinase C (PKC, not shown). Stimulation of α1-adrenoceptors causes vasoconstriction upon stimulation, leading to higher BP and increase in heart and breathing rate. (*Bottom*) Preoperative treatment options normally include α-adrenoceptor and calcium-channel blockers, which decrease Ca^{2+}-channels permeability and prevents calcium from entering the cytosol, thereby constricting blood vessels. Blockage of calcium entry relaxes and widens blood vessels. In addition, metyrosine (Demser), an inhibitor of the tyrosine hydroxylase, a rate-limiting enzyme in catecholamine biosynthesis, decreases catecholamine synthesis and therefore decreases catecholamine-induced vasoconstriction of the vessels. (*Adapted from* Malaza G, Brofferio A, Lin F, et al. Ivabradine in catecholamine-induced tachycardia in a patient with paraganglioma. N Engl J Med 2019;380(13):1284-6.)

episodic attacks do not necessarily have PCC/PGL. Similarly, a classic signature of catecholamine excess may be completely missing in patients with rare dopamine-secreting tumors. Other diseases that resemble PCC/PGL symptomatically include hypoglycemia, carcinoid syndrome, mast cell diseases, essential hypertension, panic

attacks, and cardiac arrhythmias. All of these entities should be considered in the differential diagnosis of PCC/PGL (reviewed in[43]). As a result, the expedient and accurate diagnosis of PCC/PGL is quite challenging.

PCC/PGL is diagnosed at all ages and exhibits no gender preference. The age of presentation is important, because it is likely to be informative with respect to the tumor secretion phenotype and an underlying genetic cause.[10,44] An established mutation or hereditary syndrome usually manifests at a younger age than sporadic disease. With increased referrals for genetic testing, older patients who would have otherwise been considered to have a sporadic mutation are being diagnosed with familial syndromes. Many times, older patients do not exhibit typical signs or symptoms, and tumors are often discovered serendipitously in patients with critical vascular illness, for example, stroke or heart failure with no obvious cause.[45] Hypertension can lead to a vasospasm and neurologic manifestations, such as stroke and seizures.[46] Large tumors are more commonly present in association with cardiovascular disease.[47,48]

Another challenge that could further complicate the diagnoses could arise owing to other hormones secreted in parallel with catecholamines, or induced by their excess. Some of these hormones are adrenocorticotrophic hormone that can cause Cushing's syndrome, parathyroid hormone-related peptide that can provoke hypercalcemia, vasopressin, vasoactive intestinal peptide promoting diarrhea, and growth hormone–releasing hormone that can cause acromegaly.[49–52] Catecholamines can induce abnormally high calcitonin and inhibition of insulin release, causing hyperglycemia or overt diabetes mellitus.[46] Fortunately, surgical removal of the tumor, if possible, normally alleviates these conditions. However, immediately after surgery, these patients may be at high risk for hypoglycemia because the decrease in catecholamine levels results in insulin release from the islet cells of the pancreas.

Historically, PCC/PGL came to attention in patients with symptomatic disease. However, increased use and availability of diagnostic imaging resulted in PCC/PGL being found during a hormonal evaluation for adrenal incidentalomas.[53,54] Because more patients are being evaluated by genetic counselors, diagnostic follow-up leads to tumor discovery in relatives of a patient with a known genetic mutation. Incidentally discovered tumors tend to be asymptomatic and smaller on average compared with tumors causing symptomatic disease. PCC/PGL is often associated with genetic syndromes such as MEN type 2 (MEN 2A and MEN 2B), NF-1, SDHx, and VHL syndrome. It is important for a clinician to recognize these conditions and evaluate these patients for the presence of PCC/PGL[10] (**Table 1**).

DIAGNOSIS

Who Should Be Evaluated for Pheochromocytomas and Paragangliomas?

Although clinicians are increasingly faced with the PCC/PGL in the setting of an incidentally discovered adrenal mass (eg,[55]), PCC/PGL are often diagnosed via a biochemical analysis of hormonal concentrations, followed by anatomic localization of the tumor(s). As described elsewhere in this article, PCC/PGL comes to the attention of an endocrinologist encountering patients exhibiting classic adrenergic spells (PCC/PGL triad). Subjects with a known family history (eg, *NF1*, *MEN2*, *SDHx*, and *VHL*) or those exhibiting symptoms or diagnosed for familial syndromes associated with catecholamine-secreting tumors should also be evaluated for PCC/PGL.[10,56]

Biochemical Diagnosis

The biochemical diagnosis remains the mainstay of PCC/PGL diagnosis (**Fig. 3**). Catecholamine excess indicative of an excess secreting tissue (a tumor) can be

Table 1
Genetic syndromes and clinical manifestations associated with PCC/PGL

VHL syndrome (*VHL*) VHL mutations	(PCC ~20%; ~5% malignant), angiomas, renal cell carcinoma, pancreatic cysts
MEN (type 2) syndrome *(RET)* mutations Type 2a (type 2); MEN 2A	MTC, PCC, hyperparathyroidism
MEN (type 2) syndrome *(RET)* mutations Type 2b (Type 3); MEN2B	MTC, PCC, marfanoid habitus, mucosal neuromas
NF (type 1) *(NF1)* mutations	PCC (<5%; 20% bilateral) neurofibromas, café-au-lait spots, Lisch nodules (iris hamartomas)
Succinate Dehydrogenase complex subunits B, D, C, A, AF2 (*SDHB, SDHD, SDHC, SDHA, SDHAF2*) mutations	PCC/PGL, renal cancers, GIST; pituitary adenomas
(TMEM27) mutations	PCC and rare renal cancers
(MAX) mutations	PCC/PGL
(KIF1B) mutations	PCC and neuroblastoma
(EGLN1) mutations	PCC and congenital erythrocytosis
Malate dehydrogenase (*MDH2*) mutations	PCC/PGL
Fumarate hydratase (*FH*) mutations	Rare PCC/PGL, cutaneous and uterine leiomyomas, type 2 papillary renal carcinoma
Pacak-Zhuang Syndrome (*HIF2* also known as *EPAS1*) alpha activating mutations	Somatostatinomas, PGLs, polycythemia
Carney triad (unknown genetics)	Pulmonary chondromas, GIST, extra-adrenal PGLs; in addition patients may have: adrenal cortical adenoma and esophageal leiomyoma
Carney-Stratakis syndrome (dyad) (*SDHC, SDHD, SDHB*) mutations	GIST, PGLs

Abbreviations: GIST, gastrointestinal stromal tumors; MTC, medullary thyroid carcinoma.

established by measuring levels of catecholamine (dopamine, norepinephrine, and epinephrine) metabolite products (normetanephrine for norepinephrine and metanephrine for epinephrine) in the plasma or urine.[57,58] Measuring 24-hour urine catecholamine level is important in PGL patients who do not produce norepinephrine and additional catecholamine measurements can be useful for diagnosis of dopamine-producing tumors.[59] The 2016 European Endocrine Society guidelines recommend the addition of 3-methoxytyramine test for diagnosis and follow-up of patients with PGLs; however, this test is not easily available in the United States.[37,60]

The biochemical pathway leading to the production of various catecholamines is summarized in **Fig. 4**. It begins with the conversion of tyrosine (either dietary or synthesized through hepatic phenylalanine route) into 3,4-dihydroxyphenylalanine (DOPA). This reaction is catalyzed by tyrosine hydroxylase, a rate-limiting enzyme specific for the adrenal medulla and catecholaminergic nerve terminals of the brain and sympathetic nervous system. DOPA is converted to dopamine, which becomes hydroxylated to form norepinephrine. Norepinephrine is an active hormone in some neurons of the brain and in peripheral sympathetic neurons, and it is released into circulation or the neuronal synaptic cleft upon activation. Importantly, in the chromaffin

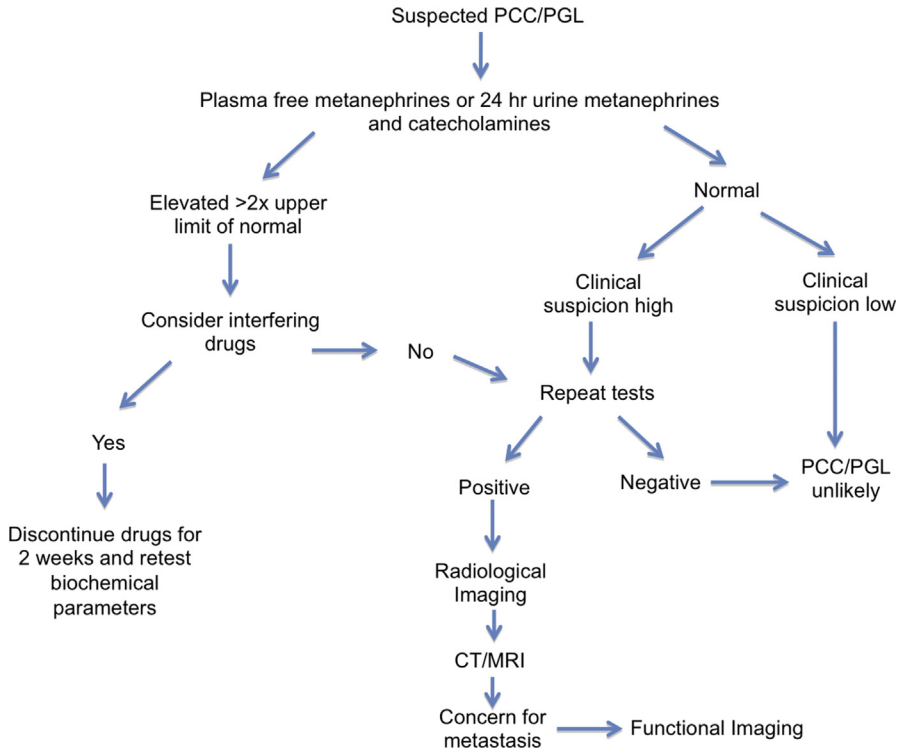

Fig. 3. A schematic diagnostic algorithm upon suspicion of PCC/PGL. CT, computed tomography.

cells of the adrenal medulla and in some neurons of central and peripheral system, PNMT (discussed elsewhere in this article) converts norepinephrine to epinephrine (adrenaline). Norepinephrine is removed from the synaptic cleft by reuptake through the norepinephrine transporter.

Most of the hormone is metabolized within the hormone-producing neuronal cells. The hormone that escapes into the bloodstream has a very short half-life and is taken up by non-neuronal cells. The turnover of norepinephrine and epinephrine by non-neuronal tissue and the adrenal medulla occurs mostly by the action of catechol-O-methyltransferase, which converts norepinephrine to normetanephrine and epinephrine to metanephrine that are known collectively as O-methylated metabolites. These metabolites are in turn oxidized by monoamine oxidase to vanillylmandelic acid. Alternatively, norepinephrine and epinephrine may be metabolized by monoamine oxidase first and later converted into vanillylmandelic acid by catechol-O-methyltransferase.[46]

Although catecholamines are secreted intermittently and have a fairly short half-life, their O-methylated derivatives are produced continuously inside tumor cells and remain relatively more stable in plasma; furthermore, the plasma metanephrine concentration is mostly independent of sympathoadrenal excitation.[61–63] Measurement of plasma high-performance liquid chromatography–fractionated metanephrines has excellent sensitivity (96%–100%) and specificity (85%–89%) as well as measuring of urinary metanephrines (sensitivity, 92%–97%; specificity, 86%–95%).[61–65] Plasma fractionated metanephrines compared with urinary metabolites seem to be less

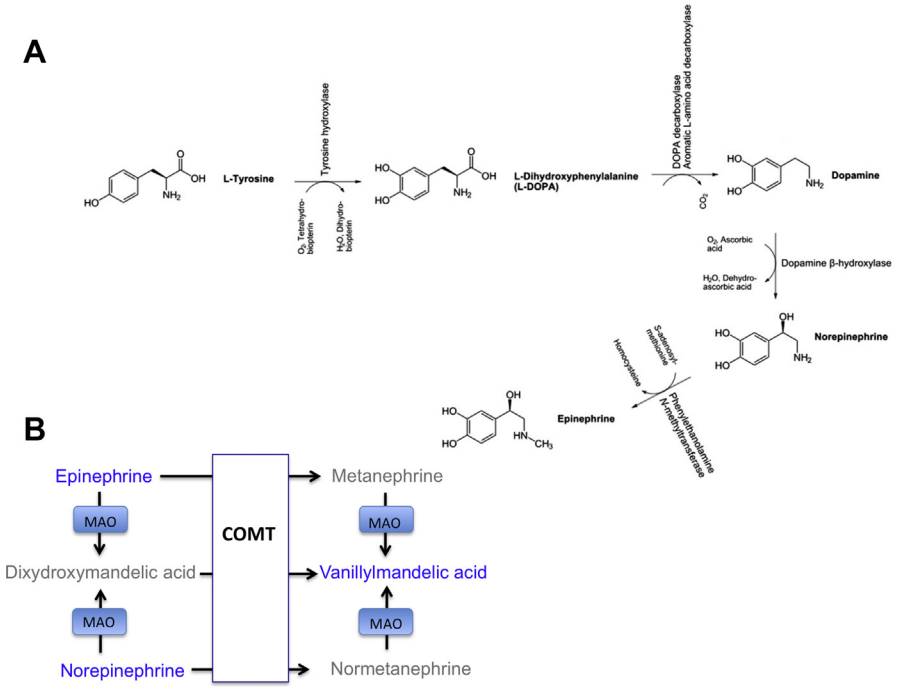

Fig. 4. The enzymes and the products of catecholamine synthesis (*A*) and degradation (*B*) in human cells. COMT, catechol-*O*-methyltransferase; DOPGAL, 3,4-dihydroxyphenylglycolaldehyde; MAO, monoamine oxidase.

affected by the concurrent use of medications (such as α- and β-blockers). An analysis of urinary vanillylmandelic acid is no longer recommended owing to reports of false-negative results.[2]

Medications (tricyclic antidepressants, levodopa, amphetamines, phenoxybenzamine, and reserpine), illness, and stress can influence concentrations of metanephrines and normetanephrines in the plasma[1,46,66] (**Table 2**); in the past, acetaminophen presence was considered to be a concern, but this is not supported by the new data for example.[67] Hence, stress-causing conditions should ideally be alleviated in advance of testing. Drugs and caffeinated beverages are known to affect

Table 2
Medications often responsible for false positive results in PCC/PGL diagnosis

Medication	High Metabolite Level (False Positive Result for PCC/PGL diagnoses)
α-Blockers	Norepinephrine, normetanephrine
Caffeine	Norepinephrine, epinephrine
Cocaine	Norepinephrine, epinephrine
Levodopa	Norepinephrine
MAO inhibitors	Normetanephrine, metanephrine
Sympathomimetics (ephedrine, albuterol, amphetamines)	Norepinephrine, epinephrine, Normetanephrine, metanephrine
Tricyclic antidepressants	Norepinephrine, normetanephrine

Abbreviation: MAO, monoamine oxidase.

catecholamine levels and these should be avoided or discontinued before biochemical testing.[46,63]

Interpretation of the results and diagnosis should take into consideration the initial level of suspicion and the degree (fold) of increase in the hormone levels. PCC/PGL in patients with cluster 2 mutations such as MEN2A, MEN2B, NF-1, and TMEM127 predominantly secrete epinephrine and metanephrine, whereas tumors within cluster 2 mutations such as SDHx, VHL, EPAS, and EGLN1 are norepinephrine and normetanephrine producing owing to lack of PNMT expression.[61,62] Additionally, PCC/PGL in patients with MEN2 normally have higher tyrosine hydroxylase activity compared with patients with VHL syndrome, accounting for higher levels of catecholamines and metabolites in MEN2 patients. Most clinicians agree that a 3- to 4-fold increase in the normetanephrine levels is affirmative of the diagnoses in a high-risk patient (eg, the one with a genetic predisposition); however, any elevation of metanephrine fraction should be carefully followed, and measurements repeated and not discarded as a false positive.[67] Similarly, normal level of metabolites in a low-risk patient could be used to exclude PCC/PGL.[64,66] The opposite outcome—positive results in a low-risk patient and negative test in a high index of suspicion patient (eg, the one with established hereditary disorder)—requires further studies before a definitive conclusion can be reached.[65] If the urine and plasma metanephrines results are ambiguous, a dynamic testing using the clonidine suppression test may be helpful for patients with norepinephrine-secreting tumors.

Localization

Diagnostic localization of a PCC/PGL is traditionally attempted only once the fact of catecholamine excess has been biochemically established. However, the quality and frequency of abdominal diagnostic imaging increase the chances for the incidental discovery of adrenal neoplasia. As a practical matter, most (approximately 85%) hormone-secreting tumors are found in the adrenal glands. The patient's age, presence of a family history, and plasma/urine hormonal levels are important in predicting the type and location of the tumor; a younger age and familial syndromes may signal extra-adrenal and/or multifocal locations.

Both computed tomography (CT) scanning and MRI are the mainstays for adrenal imaging used as the primary test for localization of catecholamine-secreting tumors. With tumors surgically confirmed, it was estimated that the sensitivity for MRI and CT to detect catecholamine-secreting tumors are 98% and 89%, respectively.[65] On CT, lipid-rich benign cortical adrenal adenomas are characterized by low unenhanced attenuation values (<10 Hounsfield units) with a rapid washout (>50% at 10 minutes) after administration of contrast medium. These tumors are usually round, homogeneous, are small (<3 cm in size), and unilateral.[68,69] In contrast, PCC almost always appear on CT scans as having high attenuation on contrast CT (>10 Hounsfield units) with less than 50% washout at 10 minutes after administration of contrast medium,[46] although some PCC may exhibit high washout (for example[70]). On MRI, lipid-rich cortical adenomas show no or only mild enhancement; in contrast, PCC/PGL show high signal intensity, especially on T2-weighted images.

If the CT scan and/or MRI fail to detect the tumor, or if there is concern that the patient has metastatic disease owing to large primary tumor size, functional localization can be attempted using a number of detecting modalities described here. This imaging takes advantage of the specific properties of the PCC/PGL related to its distinctive biochemical characteristics (reviewed in[71]).

A. PET scanning. This technology uses several radiolabeled ligands that target synthesis and metabolism of catecholamines and can be used to locate PCC/PGL tumors. The ^{18}F isotope-labeled compounds, such as ^{18}F-3, 4-dihydroxyphenylalanine (DOPA), ^{18}F-fluorodopamine (18F-FDA), or ^{18}F-fluoro-2-deoxy-D-glucose (18F-FDG) have been described in the literature; however, 18F-FDG PET is most commonly used.
B. ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy. This method uses MIBG, a norepinephrine analog with a high affinity for the norepinephrine transporter to localize the tumor.[72] It has been demonstrated that MIBG preferentially accumulates in catecholamine-producing tumors and scintigraphic localization using either ^{123}I-MIBG or ^{131}I-MIBG isotopes has been suggested for tumor localization where the results of CT/MRI studies were ambiguous. The reported sensitivity of the test is 81%, with a specificity of 99%.[73,74] Between the 2 radioisotopes, ^{123}I-MIBG is normally preferred over ^{131}I-MIBG because it allows obtaining higher quality images with a lower risk of radiation exposure.[75] Medications such as labetalol, antidepressants, and prochlorperazine are known to interfere with ^{123}I-MIBG uptake. It is recommended to discontinue these drugs 48 to 72 hours before imaging and to use an iodide preparation to protect the thyroid gland.[76] Some studies argue that there is insufficient evidence of MIBG scintigraphy value in improving diagnostic outcomes and it should be restricted to cases where radiopharmaceutical MIBG-based therapy (discussed elsewhere in this article) is to follow.[77]
C. Somatostatin receptor imaging. This approach relies on the presence of somatostatin receptors in PCC/PGL tumors.[78] ^{68}Ga-DOTATATE PET/CT scans are now being considered, especially if the tumor expresses somatostatin receptors, to detect PCC/PGL lesions as commonly seen in other types of neuroendocrine tumors such as carcinoid. This test is also instrumental for establishing the presence of functional somatostatin receptors in the tumor, which is particularly important in metastatic disease.

As with the biochemical tests, the choice of the best diagnostic imaging approach is dictated by the type of tumor. Nonfunctional imaging (CT scans and MRI) provides reasonable sensitivity and are applicable to both metastatic and nonmetastatic disease. ^{18}F-FDG is more sensitive than CT scans/MRI in detecting metastases to bone (93.7% vs 76.7%).[79–81] A new diagnostic modality for tumors expressing somatostatin receptors is ^{68}Ga-DOTATATE PET/CT imaging. In patients with malignant PCC/PGL, this approach seems to be very promising when compared with other available modalities, for example, PET or MIBG scans.[82–86] Studies are now actively being conducted to identify which subset of patients will benefit from DOTATATE imaging over other types of imaging modalities.

DISEASE MANAGEMENT

Surgery

Surgical excision remains the mainstay of management for PCC/PGL. Tumor removal not only drastically reduces the immediate negative consequences of catecholamine excess, but also leads to regression of chronic vascular and myocardial abnormalities. Evaluation of carotid intima-media thickness and left ventricular mass index in patients with PCC/PGL 5 years subsequent to tumor removal demonstrated significant improvement.[87] A comprehensive preoperative management of blood pressure is required to prevent perioperative cardiovascular complications. Several weeks of α-blockade are necessary before surgical resection of PCC/PGL. Because these patients are often volume depleted, it is important they are well-hydrated.[2,34,88,89]

Initial management normally includes an α-blocker. Phenoxybenzamine is commonly prescribed owing to its long duration of action (Fig. 5, Table 3). To counteract the tachycardia and postural hypotension sometimes resulting from the α-blocker use, β-blockers can be added on only after several days after α-blockers have been started to avoid a hypertensive crisis as a result of unopposed α-receptor stimulation. A medication such as labetalol that has action on both α- and β-receptors, also should not be started initially in a patient with PCC/PGL. Patients with PCC/PGL need at least 4:1 α- to β-blockade, and drugs such as labetalol have a 1:7 ratio α- to β-blockade. That is why it is extremely important to apply α-blocking agents first.[90] Calcium channel blockers should also be considered to block catecholamine-mediated calcium influx into vascular smooth muscle for controlling hypertension and tachyarrhythmias.[91]

The therapeutic targets of preoperative management are blood pressure less than 130/80 mm Hg and systolic pressure of greater than 90 mm Hg.[2] The advantages of perioperative management of hypertension using selective or nonselective α-blockers remain inconclusive and further studies are needed.[92–94] In any case, selective α-blocker such as doxazosin is often administered in cases where phenoxybenzamine is not well tolerated[2,34,95] (see Fig. 2, bottom). To better control blood pressure, calcium channel blockers or other antihypertensive agents (eg, tyrosine hydroxylase inhibitor, metyrosine[96]) could be added (see Table 3). Although it is necessary to take all appropriate precautions to stabilize blood pressure, peri-operative hemodynamic instability remains a major challenge.[97] Higher risk for blood pressure volatility should be anticipated in cases with larger tumor size and greater urinary/plasma metanephrine levels.[98,99]

Laparoscopic surgery is the preferred approach for PCC/PGL tumor resection.[100] As is the case with all minimally invasive approaches, this method is predictably associated with benefits for the patient (eg, shorter mean operative time and subsequent length of stay, diminished requirement for intensive care, reduced blood loss and required pain management) compared with open surgery.[95,101] Postoperative complications are more common in patients who have a history of coronary disease, experience longer duration of surgery, and blood pressure instability during surgery.[102,103]

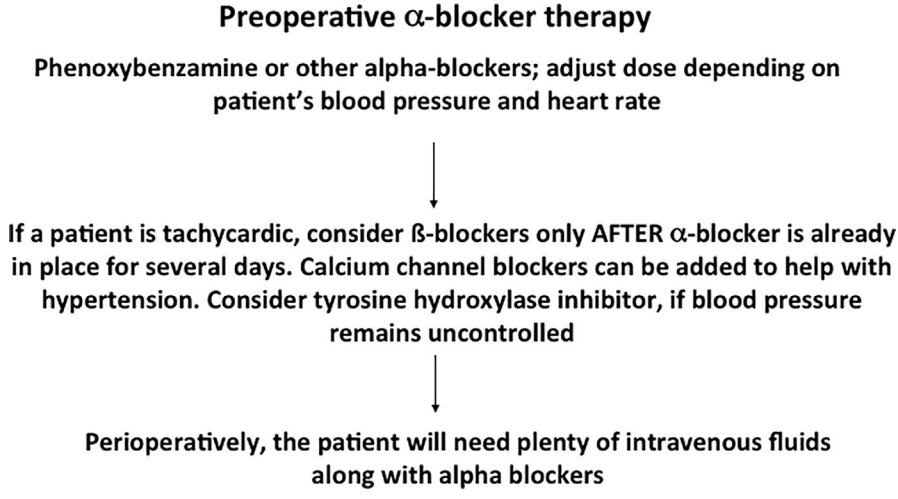

Fig. 5. A schematic preoperative algorithm for PCC/PGL.

Table 3
Common outpatient medications for management of hypertension in patients with PCC/PGL

Drug	Mechanism	Dosing	Side Effects
α-blockers			
Phenoxybenzamine	Nonselective α-blocker	Oral: Initially 10 mg twice daily, gradually increasing every other day to doses ranging between 20 and 60 mg. Some cases may require higher dosing than 60 mg/d.	Nasal congestion, tachycardia, orthostasis, nausea, and retrograde ejaculation
Doxazosin	α_1-adrenergic blocker	1–16 mg/d in divided doses 1–3 times/d	Priapism, orthostasis, edema
Terazosin	α_1-adrenergic blocker	1–5 mg/d (maximum dose 20 mg/d)	Edema, orthostasis, and tachycardia
Prazosin	α_1-adrenergic blocker	2–15 mg/d in 2–3 divided doses	Edema, orthostasis, and tachycardia
Calcium channel blockers			
Verapamil	Calcium channel blocker	120–240 mg once daily (sustained release orally)	Bradycardia, constipation, edema
Nicardipine	Calcium channel blocker	Oral: 30–60 mg twice daily	Edema, tachycardia, nausea, and sweats
Amlodipine	Calcium channel blocker	5–10 mg daily	Edema, tachycardia, headache
β-blockers			
Propranolol	Nonselective β-blocker	40–240 mg/d in 2–3 divided doses	Bradycardia, fatigue, asthma exacerbation
Metoprolol	Cardio-selective β-blocker	50–400 mg/d in 2 divided doses	Bradycardia, fatigue, asthma exacerbation
Catecholamine synthesis inhibitor			
Metyrosine (tyrosine hydroxylase inhibitor)	Tyrosine hydroxylase inhibitor	Oral: 250 mg 4 times a day; may be increased by 250–500 mg daily up to 4 g/d in divided doses	Extrapyramidal side effects and crystalluria

Open surgery is mostly recommended for large tumors (>6 cm) and multifocal PCC/PGL. Adrenalectomy and adrenocortical-sparing surgery may be performed in bilateral disease and where tumors are small.[2] Intraoperative monitoring should be performed by an anesthesiologist with experience in assisting in PCC/PGL surgeries.[104] Phentolamine therapy is a preferred route for managing hypertensive crisis, with β-blockade and other agents sometimes used to control cardiac arrhythmias (Table 4). Hypotension is often observed postoperatively and is normally sufficiently relieved by intravenous fluid therapy. Hypoglycemia could be managed through glucose administration.[2,34,95]

Palliative Management of Malignant Pheochromocytomas and Paragangliomas

Palliative surgery

Decreasing the tumor burden reduces disease severity and alleviates the symptoms owing to a decrease in hormonal synthesis from the tumor. Major risk factors are determined by the tumor type and genetic makeup. Additional factors contributing to aggressive course and excess mortality include old age, dopamine secretion, large tumor size and extensive metastases. For patients with malignant disease, open surgery is preferred because it allows for more extensive exploration, lymph node clearance, and resection of metastasis.

Palliative chemotherapy

Chemotherapy remains only partially effective in patients with malignant PCC/PGL (Fig. 6). It has been reported that treatment with a combination of cyclophosphamide, vincristine and dacarbazine chemotherapy led to partial response in 37% of 50 patients from 4 studies.[105] Partial response based on the reduction in catecholamine output had been observed in 40% of the 35 patients who were assessed. Only 4%

Table 4
Management of urgent hypertension in patients with PCC/PGL

Drug	Mechanism	Dosing	Side Effects
Phentolamine	Nonselective α-blocker	Bolus doses of 2.5–5 mg intravenously as required	Orthostasis, tachycardia and priapism
Nicardipine	Calcium channel blocker	Intravenous: start initially, 5 mg/h infusion; titrate 2.5 mg/h every 5 min (rapid titration) to 15 min (gradual titration); maximum dose is 15 mg/h; may decrease after reaching BP goal	Edema, headache, tachycardia
Nitroglycerine infusion	Nitric oxide precursor	5–100 μg/min (for hypertensive crisis)	Orthostasis, headache, tachycardia
Sodium nitroprusside infusion	Nitric oxide precursor	Intravenous: initially, 0.3–0.5 μg/kg/min; titration, increase in increments of 0.5 μg/kg/min to blood pressure target; maximum dose 10 μg/kg/min	Hypotension and cyanide toxicity
Ivabradine	Pacemaker I_f current inhibitor	5 mg orally twice a day; maximum dose 7.5 mg orally twice a day	Luminous phenomena, bradycardia, headache, dizziness

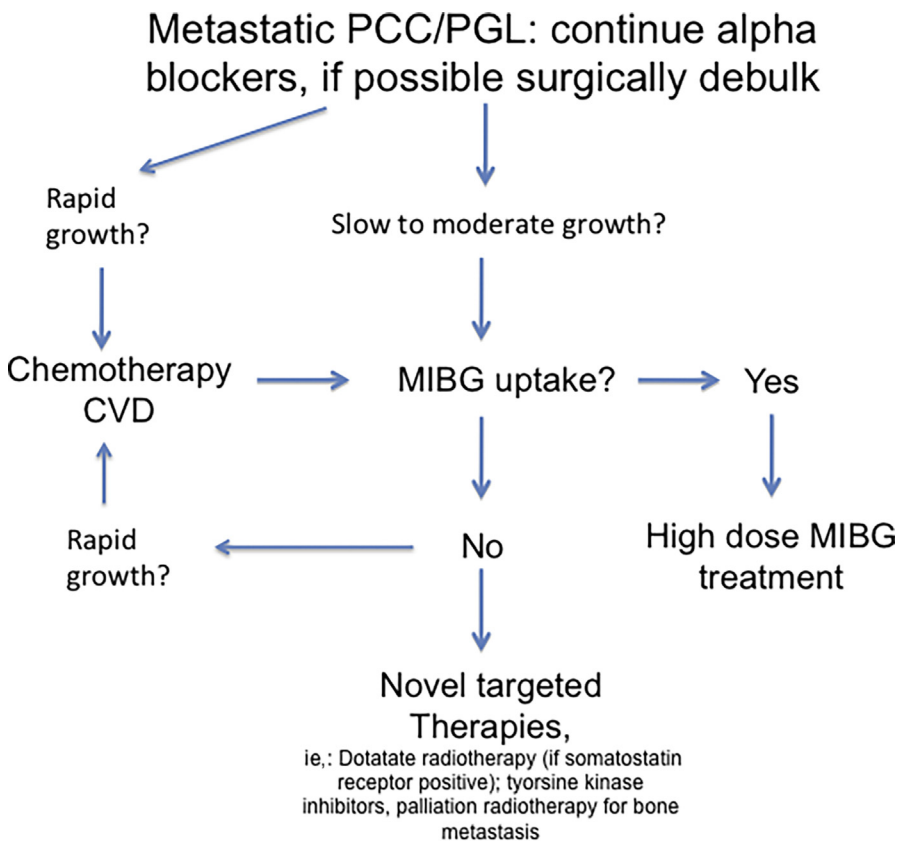

Fig. 6. A schematic management algorithm for malignant PCC/PGL. CVD, cyclophosphamide, vincristine, and dacarbazine.

of patients achieved a complete response based on tumor volume; also, toxicity led to termination of therapy in several cases. In an attempt to take advantage of the angiogenic and proliferative pathways that are activated by the genetic alterations driving PCC/PGL, angiogenic inhibitors (eg, sunitinib) have been explored in the clinic, with several of them in current clinical trials.[106–108] Considering that the mammalian target of rapamycin (mTOR) signaling pathway has been implicated through TMEM127 gene mutations,[109] other chemotherapeutic agents such as mTOR inhibitor everolimus have been tried, but so far not proven to be effective.[110] Dual mTORC1 mTORC2 inhibitors are currently being explored.[111] Other chemotherapeutic agents under current investigation for patients with malignant PCC/PGL disease include hypoxia-inducible factor-2 antagonists[112] and temozolomide.[113]

Other approaches taking advantage of diagnostic nuclear medicine have evolved into viable treatment options for patients with metastatic disease. For example, it stands to reason that MIBG can be used not only for detecting tumors (discussed elsewhere in this article), but, owing to its carrying a radioactive ^{135}I moiety, this compound can emit radiation, induce irreparable DNA damage, and promote apoptosis in cancer cells that import MIBG through their norepinephrine transporters.[114] However, unlike its established diagnostic use, a clinical role for MIBG itself was uncertain, with only 30% of patients with PCC/PGL experiencing improvement.[115]

One reason for MIBG-limited therapeutic application is an isotope exchange manufacturing method that is used for its synthesis.[116] That process inevitably leads to a mixture of isotope-labeled (hot) and unlabeled (cold) MIBG, where the unlabeled molecule is present in large excess. Cold MIBG likely competes with labeled MIBG for binding to the transporters, interfering with the uptake of active MIBG and decreasing treatment efficacy. Low specific activity of MIBG (approximately 1.59 MBq/μg) necessitates large therapeutic quantities of the compound necessary to achieve an effect.[117] At these concentrations, nonspecific effects of excess MIBG start interfering with the norepinephrine signaling and can lead to adverse cardiovascular incidents upon administration.[118]

To convert MIBG into a therapeutically promising compound, iobenguane was developed. Unlike the original compound, iobenguane ^{131}I is manufactured in a way that contains only ^{131}I-labeled molecules. It can produce a much higher radioactive (approximately 92.5 MBq/μg) dose at much lower concentration. It has been reported that iobenguane ^{131}I carries lower cardiovascular risk that classic MIBG.[119] In a trial that included 68 patients, iobenguane (Azedra) was tested for a primary outcome of at least a 50% decrease in antihypertension medications for 6 months. The secondary end point was overall tumor response measured by imaging. The study met the primary end point, with 17 of 68 patients (25%) experiencing 50% or greater reduction in all antihypertensive medication for at least 6 months. Overall tumor response was achieved in 15 of the patients (22%) studied.[120] As a result, the US Food and Drug Administration approved high-dose iobenguane for patients with metastatic PCC/PGL in 2018 (see **Fig. 6**).

Future Directions in Pheochromocytoma and Paraganglioma Treatment

Currently, clinical approaches and medicine specifically tailored toward treatment of malignant PCC/PGL starting to emerge as logical extensions of the successful diagnostic methods, improvement of existing therapies, or a combination of these strategies (reviewed in[121]). Similar to the MIBG-iobenguane paradigm, successful tumor detection using somatostatin receptor ligands (ie, ^{68}Ga-DOTATATE) offers the foundation for the related treatment strategy. So far the response rates using this type of compounds, ^{177}Lu-DOTATATE and ^{90}Y-DOTATE, in patients with PCC/PGL have been promising and further studies that involve larger patient cohorts are needed.[122–125] As newer nuclear medicine strategies are being used for treatment of metastatic PCC/PGL, it is important to be even more vigilant in controlling hemodynamic parameters. The possibility of severe hypertension and tachycardia should be considered as the tumor-produced catecholamines continue to increase, even in the patient who is well-medicated with α-blocker. An example of such a case was recently described in a patient who received ^{177}Lu-DOTATATE treatment for metastatic PCC/PGL. The patient experienced severe hypertension and tachycardia that were difficult to control with a conventional comprehensive approach, including α-blockers, calcium channel blockers, metyrosine, and β-blockers. The patient's tachycardia was finally controlled with ivabradine (Corlanor), an inhibitor of the cyclic nucleotide–gated channel residing in the sinoatrial node. Ivabradine acted to slow the sinoatrial node in the heart and lowered the heart rate.[91]

Despite recent progress in understanding the genetic and metabolic basis of PCC/PGL, no practical guidelines based on these advances have been developed for treatment of patients with malignant PCC/PGL,[126–129] and currently therapeutic approaches available for malignant disease remain noncurative. However, constantly improving fundamental knowledge of the disease provides the much-needed hope for the impending breakthrough in mechanism-guided approach for this rare cancer.

The disease associated with a germline mutation of the succinate dehydrogenase subunit B (SDHB) attracts particular attention since it is found in approximately 30% of patients with malignant PCC/PGL.[130] Tumors harboring SDHB mutations develop abnormal robust vasculature, DNA hypermethylation and upregulate genes associated with epithelial-to-mesenchymal transition, which likely promotes their dissemination.[131–134] Importantly, these tumors upregulate glucose transporters and activate glucose phosphorylation to support their metabolic needs.[135] Glucose dependence of *SDHB*-associated PCC/PGLs promotes their identification by FDG-PET.[136] FDG-PET is also an excellent read-out for the treatment success or otherwise, as reduction in glucose uptake correlates well with overall response rate in these tumors.

It is tempting to speculate that combined therapies (including those targeting universal cancer aspects of the malignant PCC/PGL) may deliver a higher rate of response and sustainable progress. The multiple drug regimen will have to be meticulously calibrated to obtain the best response while minimizing the toxicity. It is also likely that our constantly improving knowledge of PCC/PGLs will inform generation of novel, more refined and personalized approaches founded in better understanding of tumor genetics and uncover new biochemical targets to control both tumor growth and catecholamine production.

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