

Malignant Pheochromocytomas and Paragangliomas

A Phase II Study of Therapy with High-Dose ^{131}I -Metaiodobenzylguanidine (^{131}I -MIBG)

PAUL A. FITZGERALD,^{a,d} ROBERT E. GOLDSBY,^{b,d} JOHN P. HUBERTY,^c
DAVID C. PRICE,^c RANDALL A. HAWKINS,^c JANET J. VEATCH,^b
FILEMON DELA CRUZ,^b THIERRY M. JAHAN,^{a,d}
CHARLES A. LINKER,^{a,d} LLOYD DAMON,^{a,d}
AND KATHERINE K. MATTHAY^{b,d}

^a*Department of Medicine, University of California, San Francisco, California, USA*

^b*Department of Pediatrics, University of California, San Francisco, California, USA*

^c*Department of Nuclear Medicine, University of California, San Francisco, California, USA*

^d*UCSF Comprehensive Cancer Center, University of California, San Francisco, California, USA*

ABSTRACT: Thirty patients with malignant pheochromocytoma (PHEO) or paraganglioma (PGL) were treated with high-dose ^{131}I -MIBG. Patients were 11–62 (mean 39) years old: 19 patients males and 11 females. Nineteen patients had PGL, three of which were multifocal. Six PGLs were nonsecretory. Eleven patients had PHEO. All 30 patients had prior surgery. Fourteen patients were refractory to prior radiation or chemotherapy before ^{131}I -MIBG. Peripheral blood stem cells (PBSCs) were collected and cryopreserved. ^{131}I -MIBG was synthesized on-site, by exchange-labeling ^{131}I with ^{127}I -MIBG in a solid-phase Cu^{2+} -catalyzed exchange reaction. ^{131}I -MIBG was infused over 2 h via a peripheral IV. Doses ranged from 557 mCi to 1185 mCi (7.4 mCi/kg to 18.75 mCi/kg). Median dose was 833 mCi (12.55 mCi/kg). Marrow hypoplasia commenced 3 weeks after ^{131}I -MIBG therapy. After the first ^{131}I -MIBG therapy, 19 patients required platelet transfusions; 19 received GCSF; 12 received epoetin or RBCs. Four patients received a PBSC infusion. High-dose ^{131}I -MIBG resulted in the following overall tumor responses in 30 patients: 4 sustained complete remissions (CRs); 15 sustained partial remissions (PRs); 1 sustained stable disease (SD);

Address for correspondence: Dr. Paul A. Fitzgerald, Box 1222, University of California, San Francisco, San Francisco, CA 94143-1222. Voice: 415-665-1136; fax: 415-665-8500.
e-mail: paul.fitzgerald@ucsf.edu

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5 progressive disease (PD); 5 initial PRs or SD but relapsed to PD. Twenty-three of the 30 patients remain alive; deaths were from PD (5), myelodysplasia (1), and unrelated cause (1). Overall predicted survival at 5 years is 75% (Kaplan Meier estimate). For patients with metastatic PHEO or PGL, who have good ^{131}I -MIBG uptake on diagnostic scanning, high-dose ^{131}I -MIBG therapy was effective in producing a sustained CR, PR, or SD in 67% of patients, with tolerable toxicity.

KEYWORDS: malignant; pheochromocytoma; paraganglioma; MIBG

Pheochromocytomas are particularly deadly and deceptive tumors. Their production of catecholamines can cause hypertensive crisis and sudden death. Patients experience symptoms that are often mistaken for other common conditions, leading to delayed diagnoses. Malignant pheochromocytomas are even more treacherous.

Adrenal pheochromocytoma (PHEO) and extra-adrenal pheochromocytoma (paraganglioma, PGL) are rare tumors and malignant PHEOs and PGLs are extremely rare. Because few clinicians are familiar with treating patients with metastatic PHEO/PGL, a variety of management strategies have been used, with such differences probably affecting survival. This paper provides some background regarding malignant PHEO and non-head-neck PGL. We present our Phase II protocol and results to date, using high-dose ^{131}I -MIBG for treating 30 patients with metastatic PHEO/PGL and we describe our approach to overall management of these patients at the University of California, San Francisco.

BACKGROUND

Incidence of Metastatic or Multicentric Pheochromocytomas and Paragangliomas

The yearly incidence of pheochromocytoma has been reported to be 9.5/million (Minnesota),¹ 2.1/million (Sweden),² 1.5/million (Australia),³ and 1.9/million (Denmark).⁴ About 40–45% of these cases were diagnosed at autopsy. Nearly 50% of tumors are discovered incidentally during CT scanning for other reasons.⁵ At least 8% of incidentally discovered PHEO/PGL tumors have metastasized by the time of their detection.

Metastases are detected in 11% of patients with PHEOs at the time of diagnosis.⁶ PGLs are more likely to have metastasized by the time the primary tumor is discovered. Genetic syndromes, predisposing to bilateral PHEOs or multiple PGLs, commonly present in childhood. In one series of childhood cases of PHEO/PGL, 5 of 16 (31%) children were reported to have regional or distant metastases at diagnosis.⁷

Approximately 20–30% of all patients with PHEO/PGL have been found to harbor germline mutations that gives them a predisposition to develop this

tumor in multiple locations, either at the same time (synchronous) or at a later date (metachronous). Patients with genetic pheochromocytomas have been found to have metastatic or locally invasive PHEO at the time of diagnosis at the following rates: MEN 2A 4%; VHL 8%; NF-1 12%. Paragangliomas, including those associated with SDHB and SDHD mutations, are commonly malignant (30–50%). Genetic testing for SDHB mutations has proven useful, particularly for patients with metastatic PGL. When a germline defect is discovered, family members may then be screened for the mutation; carriers can have surveillance that may detect PGLs and PHEOs at earlier stages.

Metastases or additional primary tumors may not be apparent initially, because they are small or because scanning was not performed, was not sensitive for the metastases, or did not include the area of metastases in the scanning field. It is not surprising that metastases or second primary tumors are discovered in an additional 5–10% of patients, sometimes many years after resection of the primary tumor.⁸

Clinical and Histopathological Features of Malignant Pheochromocytomas and Paragangliomas

Lehnert *et al.*⁹ reviewed the diagnostic criteria for malignant pheochromocytoma. Unlike the case in most other tumors, histopathology cannot accurately determine whether a given PHEO or PGL is benign or malignant. Even the presence of vascular invasion does not predict metastases.

Efforts have been made to predict the metastatic potential of adrenal PHEOs on the basis of cases histology. The Pheochromocytoma of the Adrenal Gland Scaled Score (PASS) considers multiple factors in assessing a given adrenal pheochromocytoma's likelihood of having metastasized. Pheochromocytomas were found to be more aggressive and likely to metastasize when they had a combination of the following characteristics: vascular or capsular invasion, increased mitotic rate, atypical mitoses, necrosis, high cellularity, hyperchromasia, tumor cell spindling, large nests of diffuse growth, cellular monotony, and profound nuclear pleomorphism.¹⁰ Kimura *et al.*¹¹ recently reviewed the histology of 146 patients with PHEOs and PGLs, correlating surgical histologic with prognosis. However, no histologic scoring system is reliably accurate for determining the metastatic potential of these tumors, such that all PHEOs and PGLs must be considered potentially malignant.

Other methodologies have been used to determine a given tumor's potential for metastasis. MIB-1 nuclear proliferation marker staining was positive in 3 of 6 malignant pheochromocytomas, but in none of 45 apparently benign PHEOs in one series.¹² In another series of 92 pheochromocytomas, the 8 malignant PHEOs expressed markedly increased cyclooxygenase-2 (COX-2) activity, versus weak COX-2 activity in the 84 apparently benign PHEOs.¹³

Benign and malignant PHEOs and PGLs secrete most of the same secretory products. Serum levels of catecholamines, metanephrines, and chromogranin

A cannot reliably distinguish benign from malignant tumors prior to resection. However, when tumor markers are found to be persistently or recurrently high, months or years after the PHEO/PGL resection, metastases or new primary tumors must be suspected.

Neuron-specific enolase (NSE) is a neuroendocrine glycolytic enzyme. Serum levels of NSE have been reported to be normal in patients with benign PHEO and elevated in about half of the patients with malignant PHEO.¹⁴ However, it is possible that NSE levels are related to tumor burden, rather than malignancy *per se*; therefore, the clinical utility of NSE levels remains unproven.

At this point, only the presence of detectable metastases defines a PHEO or PGL as being malignant. However, even this feature may be misleading, because metastases may not be detected at the time of the primary tumor resection for reasons mentioned previously. Also, patients with familial germline mutations can develop new PGLs or PGLs at a later date in different locations, which may be mistaken for metastases or which may themselves metastasize. Additionally, peritoneal seeding of tumor cells at the time of surgery (pheochromocytomatosis) can cause multiple recurrences that may be mistaken for metastases.

DETECTION OF PHEO/PGL METASTASES

Urine and Blood Tumor Markers

Most patients with recurrent or metastatic PHEO/PGL have elevations in plasma or urinary normetanephrine, but some metastases from adrenal pheochromocytomas secrete mostly epinephrine and metanephrine. Plasma fractionated free metanephrines is probably the most sensitive test for detecting recurrent or metastatic PHEO/PGL, but “false positives” occur frequently. Some patients with “nonsecretory” metastases have normal plasma and urine fractionated metanephrines. Serum chromogranin A (CgA) is usually elevated in patients with both secretory and “nonsecretory” PHEO/PGL. Serum CgA is usually elevated in patients with clinically significant metastases. It is an excellent tumor marker for most patients, reflecting tumor burden.¹⁵ Fractionated urine and plasma metanephrines and serum CgA usually normalize by two weeks after a successful resection of a PHEO/PGL. However, patients with normal postoperative tests may still harbor small or nonsecretory metastases.

Detection of Metastases—Scanning

^aI-MIBG and ¹¹¹In-DTPA-Octreotide Scanning

Benzylguanidine was first developed as a guanethidine derivative for potential use as an adrenergic-blocking antihypertensive agent.¹⁶ ¹³¹I-meta-iodobenzylguanidine (¹³¹I-MIBG) was developed at the University of

Michigan for detecting adrenal pheochromocytomas.¹⁷⁻¹⁹ The usefulness of ¹³¹I-MIBG scintigraphy was confirmed at the University of California, San Francisco.²⁰ Most PHEO/PGL metastases can be detected on whole-body scintigraphy with MIBG, tagged with a radioisotope of iodine.^a ¹²³I-MIBG scanning with single-photon emission computed tomography (SPECT) is more sensitive than ¹³¹I-MIBG planar imaging, particularly for PGLs and metastases.²¹ Despite the value of I-MIBG in diagnostic scanning for PHEO/PGL, only about two-thirds of metastases are avid for MIBG. Patients with metastases that are avid for *I-MIBG often harbor concurrent metastases or second primaries that are not avid for *I-MIBG and may remain undetected even on post-therapy whole-body scanning after high-dose ¹³¹I-MIBG therapy.

There are other problems with *I-MIBG scanning. Patients may have significant bowel activity that may be mistaken for an abdominal paraganglioma or metastasis. Delayed imaging after a laxative is sometimes required in these patients. Because MIBG is excreted in the urine, bladder paragangliomas may not be visualized or may be mistakenly thought to have *I-MIBG uptake. ¹²³I-MIBG SPECT imaging of the bladder during bladder irrigation is sometimes required to elucidate this situation. Another nuclear imaging technique used to locate metastases is ¹¹¹In-DTPA-octreotide, which is reported to have a sensitivity of only 44%, but often detects metastases that are not visualized with *I-MIBG.

PET Scanning

Positron emission tomography (PET) is the most sensitive scanning technique for imaging PHEO/PGL metastases. PET scanning dramatically displays metastatic tumor burden and the response to therapy.²²

PET scanning with ¹⁸F-deoxyglucose (¹⁸FDG) works on account of the fact that deoxyglucose is absorbed into cells by a glucose transporter and accumulates in the cells because it cannot enter glycolytic pathways. An estimated 90% of PHEO and PGL metastases are avid for ¹⁸FDG. However, ¹⁸FDG PET is nonspecific and may detect other tumors and has increased uptake in areas of increased glucose absorption, such as the brain, inflammation, muscle activity, or bone marrow after G-CSF stimulation.

¹⁸F-dopamine PET scanning is both highly sensitive and specific for primary PHEO/PGL and metastases. Although both ¹⁸F-dopamine and *I-MIBG are transported into cells by an amine uptake-1 mechanism, ¹⁸F-dopamine is more actively transported into neurosecretory vesicles, where it is stored, whereas *I-MIBG may leave the cell. Therefore, ¹⁸F-dopamine PET scanning is more sensitive than even ¹²³I-MIBG SPECT scanning. ¹⁸F-dopamine PET scanning is more selective than ¹⁸FDG-PET for PHEO/PGL metastases, as well as being about 90% sensitive. However, ¹⁸FDG PET scanning may underestimate the

^aI = either ¹²³I or ¹³¹I

number of metastases in patients with advanced metastases and a high tumor burden. Also, false-positives may occur with ^{18}F FDG PET, such as gallbladder visualization.²³

Disadvantages of PET scanning include its high cost and radiation exposure. Both ^{18}F FDG and ^{18}F -dopamine PET scanning can be combined with CT scanning to produce extraordinarily accurate anatomic imaging. Combined PET/CT fusion imaging is currently the state-of-the-art for accurately detecting and quantifying PHEO/PGL metastases.

CT Scanning

CT scanning without contrast is helpful in determining the density of adrenal nodules, which is measured in Hounsfield Units (HUs). Adrenal nodules with densities above 10–25 HUs ordinarily are seen with PHEOs, excluding adrenal adenomas and lipomas, but high HU density is seen with other tumors. A mass with a low density of <10 HU on noncontrast CT is not likely a PHEO/PGL. For CT scanning with intravenous contrast enhancement, nonionic contrast is preferred, because it is unlikely to induce hypertensive crisis.²⁴

MRI Scanning

MRI scanning can be helpful, particularly for imaging bone and hepatic metastases, given most PHEO/PGLs display increased signal intensity on T₂-weighted imaging. MRI is also preferred for children and pregnant women, due to lack of radiation exposure.²⁵

These different scanning techniques can be considered complementary to each other, with no single imaging modality being 100% sensitive and specific for metastatic PHEO or PGL.

Differential Diagnoses for Metastatic PHEO and PGL

The differential diagnosis for apparent PHEO/PGL metastases includes benign paragangliomas, multicentric paragangliomas, second pheochromocytomas, intraperitoneal seeding (pheochromocytomatosis), false-positive scanning, and other malignancies. Patients with VHL germline mutations may have a concurrent renal cell carcinoma and hemangioblastomas. Patients with MEN-2 may have concurrent medullary thyroid carcinoma. Patients with NF-1 usually have concurrent neurofibromas and may develop gliomas and malignant peripheral nerve sheath tumors (MPNSTs, neurofibrosarcoma). Any suspicious mass lesion that is not demonstrated on ^{123}I -MIBG or ^{18}F -dopamine PET scanning should be considered for a CT-guided fine-needle aspiration biopsy for definitive diagnosis.

Historical Prognosis for Patients with Benign and Malignant PHEOs and PGLs

Patients with benign pheochromocytomas have an increased mortality rate. Although the perioperative mortality rate for patients undergoing unilateral benign adrenal PHEO resection is now only about 3% with optimal medical preparation, anesthesia, surgical, and postoperative care, these patients experience a long-term mortality rate that is higher than that of age-matched controls. A Swedish series of 121 patients with pheochromocytoma reported no peri-operative mortality, but 50% of patients remained hypertensive postoperatively. Of the 121 patients, 42 died during a period averaging 15 years, versus an expected 23.6 deaths in an age-matched general population, yielding a 78% increase in mortality (RR = 1.78). Of the 42 patients who died, 20 deaths were due to cardiovascular disease, 6 from associated neuroectodermal tumors, 5 from other malignancies, 7 from unrelated causes, and 4 from malignant pheochromocytoma.²⁶

Patients with metastatic PHEO/PGL, treated with conventional radiation and chemotherapy, have been reported to have a mean 5-year survival rate of about 44%. However, survival can vary from days to decades. The prognosis is worse for those patients whose metastatic disease is discovered at a late stage and those with diffuse pulmonary metastases. Malignant PHEO/PGLs vary tremendously in their aggressiveness, secretory capacity, and sites of metastases. These variables affect each patient's prognosis.

Treatment—Medical Therapy

Bravo has reviewed antihypertensive therapy for patients with pheochromocytoma.²⁷ About 50% of patients with PHEO/PGL metastases have persistent hypertension after resection of the primary tumor. Hypertensive patients must be involved with home blood pressure monitoring with an accurate automatic sphygmomanometer (arm cuff). Blood pressures should ideally be determined at home once or twice daily and immediately in the event of acute symptoms of headache, perspiration, palpitations, or other unique symptoms that the patient experiences with hypertensive episodes. While phenoxybenzamine is effective and tolerable for short periods preoperatively, most patients experience side effects from phenoxybenzamine, such as fatigue and nasal congestion, making the drug less suitable for chronic therapy. Phenoxybenzamine accumulates in the fetus more than it does the mother, with a fetal:maternal concentration ratio of 1.6:1 and has been associated with neonatal hypotension in the newborn.²⁸

Calcium channel blockers are effective and usually tolerated better than alpha blockade. They may be used alone or in combination with tolerated doses of alpha-blockers or other antihypertensives. Calcium channel blockers were used successfully as the sole peri-operative management in a French

study involving 105 surgeries for pheochromocytomas and paragangliomas. Both nifedipine and nifedipine have been used extensively.^{29,30} Blake *et al.*³¹ reported the results of using nifedipine to treat five patients with metastatic PHEOs. In one patient, there was a remarkable and reproducible doubling of the tumor-absorbed dose of ¹³¹I-MIBG due to prolonged tumoral retention of the isotope; nifedipine also caused this patient's norepinephrine excretion to decline by two-thirds.

Nifedipine is also useful for treating acute hypertensive events in the hospital (during procedures or ¹³¹I-MIBG infusion therapy) or at home. Hypertensive patients with metastatic or unresectable secretory PHEO/PGLs are given a supply of nifedipine-10-mg capsules; if the patient measures a blood pressure that exceeds 170 mm Hg, and immediately verifies it, he is instructed to chew one pierced capsule and monitor his blood pressure carefully.

Other antihypertensive medications may be effective as add-on therapy for hypertensive patients with malignant pheochromocytoma or paraganglioma. Elevated catecholamine levels stimulate renin secretion, which increases angiotensin II production and aggravates hypertension. Adding an angiotensin receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor is often an effective measure. Besides the usual antihypertensive measures, intravenous magnesium sulfate has proven effective in children and pregnant women.³²

Beta-blocker therapy is given to patients with sustained tachycardia or intermittent tachyarrhythmias, after initiation of antihypertensive therapy. Sustained-action cardio-selective beta-blockers are preferred, such as metoprolol XL. Labetalol is avoided, since it causes misleading elevations in urinary catecholamine determinations in some assays. Labetalol also interferes with norepinephrine uptake-1, and patients taking labetalol should discontinue the drug for at least one 4–7 days before ¹⁸F-dopamine PET, ¹²³I-MIBG scintigraphy or ¹³¹I-MIBG therapy.³³

Metyrosine partially inhibits tyrosine kinase and tumoral catecholamine secretion; metyrosine does not inhibit norepinephrine uptake-1 and ¹³¹I-MIBG scanning and therapy can be used in patients being treated with metyrosine. However, metyrosine does not inhibit tumor growth and its side effects are considerable, exerting an adverse impact on the patient's well-being such that metyrosine therapy is not generally advisable.³⁴

Patients with functioning malignant PHEO/PGLs are advised to observe certain precautions. Patients are advised to avoid activities that might put physical pressure on large soft tissue tumors, precipitating catecholamine release, and hypertensive crisis. Patients must be counseled to avoid decongestants, cocaine, diet pills, MAO inhibitors, and other drugs that can provoke a hypertensive crisis. Epinephrine, injected by dentists and emergency physicians to help retain local anesthesia, may also precipitate symptoms in patients with secretory metastases. Intravenous ionic contrast for CT scanning may precipitate hypertensive crisis in patients with secretory tumors; however, nonionic intravenous contrast appears to be relatively safe.³⁵

Treatment—Surgery

For patients having what appears to be an isolated adrenal pheochromocytoma, a total adrenalectomy is more likely to prevent recurrence than a selective adrenal-sparing surgical procedure,³⁶ which is sometimes attempted for patients with bilateral pheochromocytomas or familial disease. For patients who are found to have metastases at the time of diagnosis, it is usually best to resect the primary tumor as well as large metastases. Laparoscopic adrenalectomy has become the procedure of choice for pheochromocytomas up to 5 to 6 cm in diameter.^{37,38} Large cranial, abdominal, and pulmonary metastases have been successfully resected. The surgical reduction of tumor burden can reduce symptoms and is presumed to prolong survival. These tumors can be indolent and debulking improves local symptoms, catecholamine levels and hypertension. Lower plasma norepinephrine levels may possibly improve *I-MIBG uptake-1, especially when postoperative plasma norepinephrine levels are below 500 ng/mL.³⁹

Some tumors, particularly retroperitoneal paragangliomas in the abdomen or pelvis, can become massive, encasing major blood vessels and other organs. Heroic surgery may require vascular grafts, ureter stenting, nephrectomy, and other procedures. Surgical resection of massive paragangliomas can be extremely difficult and the patients must be rendered normotensive preoperatively. Perioperative intensive monitoring and treatment by an experienced anesthesiologist and surgical team are mandatory. Even so, surgical complications are common. Postoperative pulmonary embolism from pelvic veins is particularly common in patients with massive abdominal or pelvic tumors. Therefore, women should discontinue oral contraceptives 2 months preoperatively and all such patients should be treated with low-molecular-weight heparin postoperatively.

Large invasive pheochromocytomas and paragangliomas are extremely vascular, causing serious problems with hemostasis and making tumor resection difficult and sometimes impossible. Preoperative arterial embolization has proven feasible for some secretory tumors. However, some large tumors cannot be resected, particularly massive retroperitoneal paragangliomas that have encased major blood vessels and involve other organs. Many patients have metastases that are so massive or numerous that surgical debulking is impossible. In these cases, non-surgical approaches to treatment are of the first order.

Treatment—Chemotherapy

The most commonly used chemotherapy regimen for patients with metastatic PGL or PHEO, reported by Averbuch *et al.*⁴⁰ uses a combination of cyclophosphamide, vincristine, and dacarbazine/DTIC (CVD). Cyclophosphamide 750 mg/m² and vincristine 1.4 mg/m² are given on day 1, and dacarbazine 600 mg/m² is given on days 1 and 2. The cycle is repeated every 21 days. This

chemotherapy regimen, given every 21 days, was reported to cause complete or partial remissions in 7 of 12 patients (57%).

In a review of chemotherapy for patients with metastatic paraganglioma, 5 of 11 achieved a partial remission after various regimens, including: cyclophosphamide, doxorubicin, and DTIC/dacarbazine (CyADIC); cyclophosphamide, vincristine, doxorubicin, and DTIC/dacarbazine (CyVADIC); doxorubicin and dacarbazine (ADIC).⁴¹

Despite some success with chemotherapy for patients with malignant pheochromocytoma, continuous cycles must be given on a long-term basis, because tumors usually recur during necessary or patient-requested “breaks” in chemotherapy. Chronic chemotherapy has an adverse impact on quality-of-life, because most patients experience recurrent bouts of malaise, nausea, or other adverse reactions after each cycle. Cyclophosphamide can cause sterility, myelosuppression, nausea, alopecia, hemorrhagic cystitis, cardiomyopathy, stomatitis, darkened skin and nails, and an increased risk for second malignancies. Vincristine neurotoxicity can lead to severe peripheral neuropathy with pain, cranial nerve palsies, severe muscle weakness, intestinal ileus and, rarely, ataxia. Dacarbazine can cause myelosuppression, nausea, myalgias, fever, diarrhea, photosensitivity, hepatic and renal dysfunction, and occasional anaphylaxis. Doxorubicin can cause cardiomyopathy and ventricular arrhythmias, myelosuppression, alopecia, onycholysis, nausea, severe stomatitis, esophagitis, and necrotizing enterocolitis. Side effects related to chemotherapy can reduce compliance with repeated cycles of therapy. Nevertheless, many patients do exhibit partial responses to chronic chemotherapy and some patients appear to tolerate it reasonably well.⁴²

Zoledronic acid is a third-generation bisphosphonate. Patients with bone metastases are empirically treated with zoledronic acid (Zometa), 4 mg infused intravenously over 20 min. The frequency of the zoledronic acid infusions has varied, being given every 1 to 12 months, depending upon the extent and aggressiveness of the bone metastases and the patient’s tolerance for the treatment. Zoledronic acid inhibits osteoclastic bone resorption and has proven useful for other malignancies that metastasize to bone.⁴³ Zoledronic acid has been reported to provide effective treatment for bone metastases from a variety of tumors, such as breast cancer, prostate cancer, renal cell carcinoma, multiple myeloma, chronic myeloid leukemia, and Ewing’s sarcoma. However, there are no data for the effectiveness of zoledronic acid for osseous metastases from pheochromocytoma. Zoledronic acid therapy is generally well tolerated, with the exception of transient flu-like symptoms (that may be severe) within a week following the infusion; hypocalcemia and thrombotic thrombocytopenic purpura, and jaw osteonecrosis occur rarely.

Treatment—Potential Anti-VEGF/VEGFR and Adjuvant Therapies

Vascular endothelial growth factors (VEGFs) are pro-angiogenesis molecules. VEGFs bind to vascular VEGF receptors (VEGFRs), causing

receptor dimerization and activation of receptor tyrosine kinase that induces vascular proliferation, a necessary process for tumorigenesis and metastasis. VEGFs are over-expressed in about 70% PGLs⁴⁴ and are also over-expressed in PHEOs.^{45–47} Mutations in the gene encoding mitochondrial succinate dehydrogenase subunit B (SDHB) in PGLs activate cellular hypoxia pathways that stimulate the production of VEGFs.⁴⁸ Middeke *et al.*⁴⁹ have demonstrated the importance of VEGF for PHEO angiogenesis *in vitro*.

Potential anti-VEGF drug therapies include monoclonal antibodies against VEGF. Zielke, *et al.*⁵⁰ demonstrated that antibodies to VEGF inhibited PHEO tumor growth, both *in vitro*, and *in vivo*. A VEGF monoclonal antibody, bevacizumab, has been approved by the FDA as a first-line treatment for colorectal cancer.⁵¹

New cancer therapies are targeting VEGF receptors (VEGFRs). Inhibitors of VEGFR-2 may preferentially target tumor vasculature.⁵² The initial clinical trials of VEGFR-2 inhibitors were disappointing. However, the results from ongoing clinical trials of second-generation oral VEGFR-2 inhibitors (e.g., ZD6474), for other solid tumors, have been more encouraging.^{53,54}

Cyclooxygenase-2 is over-expressed in PHEO/PGL¹³ and Cox-2 inhibitors might be helpful in reversing resistance to chemotherapy.⁵⁵ Nifedipine may improve the therapeutic uptake of ¹³¹I-MIBG into PHEO/PGL metastases in certain patients.³¹ Starikova *et al.*⁵⁶ demonstrated that nifedipine reduced the mitotic rate and proliferation of PC-12 cells *in vitro*.

Clinical trials of such potential anti-VEGF/VEGFR and adjuvant therapies are required for patients with metastatic PHEO/PGL.

Treatment—Radiation Therapy

External beam radiation therapy completely abolishes tumoral avidity for MIBG and renders subsequent *I-MIBG scanning insensitive and makes ¹³¹I-MIBG ineffective therapy for irradiated metastases. Therefore, if ¹³¹I-MIBG therapy is planned, radiation should not be given to metastases displaying *I-MIBG avidity prior to ¹³¹I-MIBG therapy. External beam radiation therapy may be given subsequently to osseous metastases, if ¹³¹I-MIBG therapy is ineffective. Radiation therapy has proven moderately efficacious for relieving pain and inhibiting the growth of bone metastases.⁵⁷ Radiation therapy to large cranial bone metastases can produce neurologic improvement. Large abdominal or pelvic paragangliomas generally should not be irradiated, because such radiation is not particularly effective, causes gastrointestinal disturbance, and makes later surgeries relatively contraindicated due to the risk of wound dehiscence, abscesses, and fistulas. Certain small recurrent tumors may be amenable for treatment with CyberKnife stereotactic radiosurgery. It may be useful for localized spinal metastases and can be used for recurrent growth of bone metastases in a previously irradiated field. Cyberknife also carries the advantage to the patient of being given in a single day, rather than

over the 5 weeks typically required for conventional external beam radiation therapy.⁵⁸

¹³¹I-MIBG Therapy—History

Metaiodobenzylguanidine bears a structural resemblance to norepinephrine (FIG. 1). From pharmacologic studies, benzylguanidine was found to participate in both uptake pathways by adrenal medullary cells, where it is subsequently stored in neurosecretory granules. Because of the effectiveness of ¹³¹I for the treatment of thyroid cancer, higher doses of ¹³¹I-MIBG for treatment of patients with malignant pheochromocytoma was first used at the University of Michigan and reported in 1984.⁵⁹ Two of five patients achieved partial remissions after total doses of 373–484 mCi ¹³¹I-MIBG, fractionated as 3–4 separate treatments. Since then, many other patients with malignant PHEO/PGL have been treated with ¹³¹I-MIBG elsewhere.^{60–66}

Many nonfunctioning PHEO and PGL metastases continue to exhibit norepinephrine uptake-1, such that treatment with ¹³¹I-MIBG can be effective for patients with nonfunctioning tumors, as long as scanning demonstrates that the tumors are avid for MIBG. Following therapy with ¹³¹I-MIBG, once background radiation has dissipated, a post-treatment whole-body scan can be obtained that indicates the successfulness of the treatment and may locate the presence of metastases that were not appreciated on diagnostic ¹²³I-MIBG scanning.

Competitive inhibition of tumoral uptake of ¹³¹I-MIBG may be caused by the large amount of “cold” ¹²⁷I-MIBG that is also infused, a product of the current

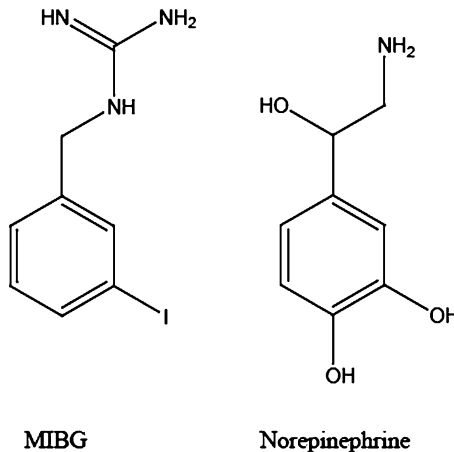


FIGURE 1. Molecular diagrams of metaiodobenzylguanidine and norepinephrine.

exchange labeling method of synthesizing ^{131}I -MIBG. The “no-carrier-added” method of synthesizing ^{131}I -MIBG produces less cold ^{127}I -MIBG. Mairs *et al.*⁶⁷ demonstrated that human neuroblastoma xenografts in nude mice had better uptake of no-carrier-added ^{131}I -MIBG than conventional exchange-labeled ^{131}I -MIBG; however, uptake was also increased in the adrenal and heart. No-carrier-added ^{131}I -MIBG is being developed commercially and clinical trials are under way to determine whether it is superior to exchange-labeled ^{131}I -MIBG for treating patients with malignant PHEO/PGL.

Peripheral Blood Stem Cell (PBSC) Leukapheresis and Cryopreservation

PBSC leukapheresis is now widely available and is used for patients with other malignancies before they receive myeloablative chemotherapy. Marrow stimulation with granulocyte colony-stimulating factor (GCSF) allows successful PBSC harvesting in most patients, usually after 1–2 leukapheresis sessions. The reinfusion of the patient’s own cryopreserved PBSCs has been extremely effective and engraftment has been successful in over 95% of cases. In 1998, Matthay *et al.*⁶⁸ at the University of California, San Francisco, reported a Phase I dose escalation of ^{131}I -MIBG with autologous bone marrow support in refractory neuroblastoma. Sung *et al.*⁶⁹ reported the use of autologous stem cell transplantation after high-dose chemotherapy in patients with high-risk neuroblastoma.

Patients with extensive PHEO/PGL bone metastases can have bone marrow involvement with tumor, such that tumor cells could be inadvertently harvested along with the PBSCs during the leukapheresis procedure. Such marrow involvement is a relative contraindication to PBSC leukapheresis. Advances in purging the harvested PBSCs of tumor cells have been reported.⁷⁰

High-Dose ^{131}I -MIBG Therapy—The UCSF Experience

A Phase I-II dose-escalation protocol for ^{131}I -MIBG therapy for patients with malignant pheochromocytoma and related tumors was begun in 1991 at the University of California, San Francisco (UCSF). A concurrent UCSF Phase I pediatric oncology protocol investigated the use of ^{131}I -MIBG therapy for children with malignant neuroblastoma. In 1997, on the basis of the Phase I toxicity dose escalation studies, the protocol was revised and formally entered Phase II.

In 2003, Rose *et al.*⁷¹ described the experience with the first 12 patients with metastatic pheochromocytoma treated with high-dose ^{131}I -MIBG therapy at the University of California, San Francisco. Of these 12 patients, 5 had received prior external beam radiation and/or chemotherapy. Their median single treatment dose was 800 mCi (37 GBq) or 11.5 mCi/kg (ranges,

386–866 mCi or 6.6–18.3 mCi/kg). Their median cumulative dose was 1015 mCi (range, 386–1690 mCi). Three of the twelve patients had complete responses; two had soft-tissue and skeletal metastases and one had intraperitoneal seeding of tumor, with recurrent disease. Seven patients had a sustained partial response (PR), two had an initial PR with progressive disease (PD) and death at 13 and 11 months, respectively. Two patients did not respond and died with PD. Grade 3 thrombocytopenia followed 79% (15 of 19) of ^{131}I -MIBG treatments. Grade 3 and 4 neutropenia followed 53% and 19% of treatments, respectively.

We have now treated 32 patients for our ongoing Phase II trial. Of these patients, we have post-therapy data to evaluate the responses of 30 patients. All patients had surgery for their primary tumor and had unresectable metastases. These 30 patients met strict eligibility criteria (TABLE 1).

Of these 30 patients, there were 19 males and 11 females. Ages ranged from 10 to 62 years (mean 39 years; seven patients were under age 18 years). Nineteen patients had paragangliomas: 10 juxta-renal, 8 periaortic/aortic bifurcation, 2 pelvis, 1 atrium/mediastinum, 1 lung apex/perivertebral. Four of seven patients with paragangliomas, who have had genetic testing, have been found to harbor germline mutations in the gene encoding succinate dehydrogenase subunit B (SDHB). Eleven patients had pheochromocytomas: seven of the left adrenal, four of the right adrenal. Distant metastases were present in 27 of the 30 patients (90%) (TABLE 2).

High-dose ^{131}I -MIBG resulted in the following overall tumor responses in these 30 patients: 4 sustained complete remissions (CR); 15 sustained partial remissions (PR); 1 sustained stable disease (SD); 5 had initial PR or SD, but relapsed to progressive disease (PD); 5 had PD. Patient follow-up has ranged from 7 to 154 months. The criteria for remission are listed in TABLE 3. Patients with sustained remission were noted to have a gradual response to high-dose ^{131}I -MIBG, with improvements in tumor markers and scans continuing for up to 24 months in some patients (FIG. 2).

Of the 30 treated patients, 23 remain alive. Dating from the time of initial ^{131}I -MIBG therapy, overall survival at 5 years has been 75% by Kaplan-Meier estimate (FIG. 3). Of note, there was a considerable delay between the diagnosis of the primary tumor and the time of ^{131}I -MIBG therapy: median, 68 months; mean, 45 months; range, 2 to 310 months.

Eight patients have died. One patient died from a non-tumor-related cause after a sustained PR. Another patient died after a PR lasting 5 years, at which time she developed PD and myelodysplastic syndrome with monosomy 7, a known potential risk for ^{131}I -MIBG therapy.^{72–74} This patient died suddenly and unexpectedly during myeloablative therapy and allogenic marrow transplant. Six of the 30 patients have died from aggressive progressive disease (PD). Five of these six patients had abdominal or pelvic paragangliomas as their primary tumor.

TABLE 1. Eligibility criteria for high-dose ^{131}I -MIBG therapy for patients with metastatic pheochromocytoma or paraganglioma—UCSF Phase II Protocol***Inclusion criteria***

- Histological documentation of pheochromocytoma or paraganglioma.
- Tumor not amenable to surgical excision.
- Tumor with *I-MIBG avidity that is at least twice background.
- >3 weeks since chemotherapy.
- >2 weeks since major surgery.
- >4 weeks since completion of prior radiation therapy; no radiation therapy for 4 months after ^{131}I -MIBG, except for progressive disease.
- No treatment with an investigational agent concurrently or within 30 days before therapy.
- Patients who have received previous chemotherapy or radiation therapy must have evidence of persistent disease on *I-MIBG scan and elevated tumor markers or measurable lesions by CT/MRI before receiving high-dose ^{131}I -MIBG.
- ≥ 4 years of age.
- Agreement to use birth control for at least 2 months before (women) and for at least 6 months after (men and women) ^{131}I -MIBG therapy.
- Required initial laboratory data (minimum levels):
 - Neutrophil count $\geq 1,000/\mu\text{L}$
 - Platelet count $\geq 80,000/\mu\text{L}$
 - AST (SGOT) $\leq 2.5 \times \text{ULN}$
 - Total bilirubin $\leq 2.5 \times \text{ULN}$
 - Creatinine $\leq 2 \times \text{ULN}$

Measurable tumor

- Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as >10 mm as measured with CT/MRI scanning, *OR*
- Lesions <10 mm diameter or bone lesions in the presence of demonstrable uptake of *I-MIBG on diagnostic scanning, plus elevated levels of a tumor marker specific for pheochromocytomas: urine catecholamines or metanephrines or serum CgA.

Exclusion criteria

- Estimated life expectancy <12 weeks.
- Karnofsky performance status <60%.
- Psychiatric illness that precludes informed consent.
- Pregnancy or nursing.
- Brain lesions that are parenchymal and MIBG-avid.
- Uncontrolled intercurrent illness, including but not limited to: ongoing active infections, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- Second Malignancies:
 - Patients with a “currently active” second malignancy, other than non-melanoma skin cancers, are not eligible.
 - Patients are not considered to have a “currently active” second malignancy if they have been cancer-free for ≥ 5 years.

TABLE 2. Sites of metastases in 30 patients with metastatic paraganglioma or pheochromocytoma—UCSF Phase II Protocol

-
- Distant metastases: 27/30 = 90%
 - Bone: 23/30 = 77%
 - Liver: 12/30 = 40%
 - Local nodes (in addition to distant metastases): 11/30 = 37%
 - Distant nodes: 6/30 = 20%
 - Lungs: 4/30 = 13%
 - Muscle: 3/30 = 10%
 - Pituitary: 1/30 = 3%
 - Local metastases only: 3/30 = 10%
 - Local nodes: 2/30 = 6%
 - Peritoneal seeding: 1/30 = 3%
-

UCSF Protocol for ¹³¹I-MIBG Therapy

Peripheral Blood Stem Cell (PBSC) Leukapheresis and Cryopreservation

Patients who are candidates for high-dose ¹³¹I-MIBG have a PBSC leukapheresis prior to therapy. PBSC leukapheresis is now widely available and is used for patients with other malignancies before they receive myeloablative chemotherapy. Marrow stimulation with granulocyte colony-stimulating factor (G-CSF) allows successful PBSC collection in most patients, usually after 1–2 leukapheresis sessions. Cyclophosphamide rebound has not been required for successful PBSC harvesting in patients with metastatic PHEO and PGL. The reinfusion of the patient's own cryopreserved PBSCs has been extremely effective with successful engraftment in over 95% of cases.

Patients with extensive PHEO/PGL bone metastases may have bone marrow involvement with tumor, creating a risk that tumor cells could be inadvertently harvested along with the PBSCs during the leukapheresis procedure. Therefore, patients with significant bone metastases have a bone marrow biopsy prior to PBSC harvest to help determine whether the marrow is involved

TABLE 3. Definitions of tumor responses—UCSF Phase II Protocol

Complete response (CR): Sustained disappearance of all lesions visible on *I-MIBG scan and CT/MRI scan and normal catecholamines, metanephrines, and CgA.

Partial response (PR): Sustained decrease in metastases visible on *I-MIBG scan, and $\geq 30\%$ reduction in the sum of the longest diameter of soft-tissue metastases, and $\geq 50\%$ decrease in initially-elevated catecholamines, metanephrine, and CgA.

Stable disease (SD): No significant change in *I-MIBG scan, no change in CT/MRI of metastases, no change in tumor markers to qualify for PR or PD.

Progressive disease (PD): New metastases on *I-MIBG scan, or increase of $\geq 20\%$ increase in maximum diameter of metastases or new metastases on CT/MRI scan, or $> 20\%$ increase in initially-elevated catecholamines, metanephrines, or serum CgA levels.

PR/SD \rightarrow PD: Initial PR or SD relapsing to PD.

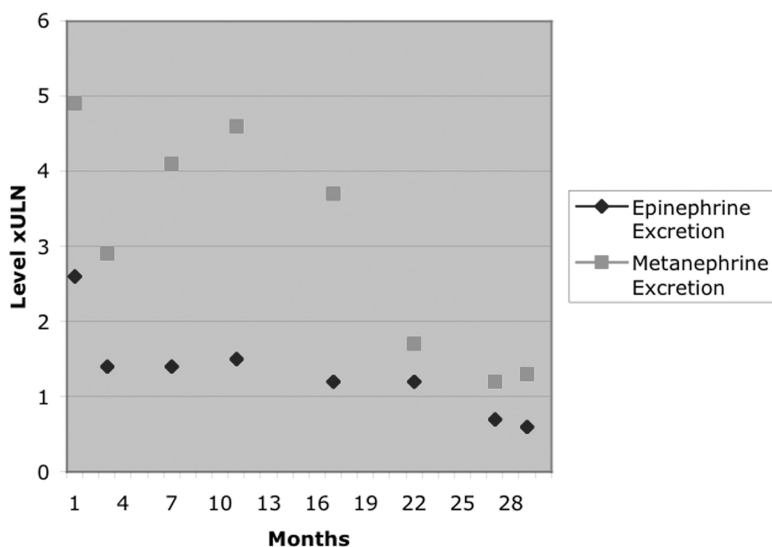


FIGURE 2. Plot of urinary epinephrine and metanephrine excretion in a patient with metastatic adrenal pheochromocytoma, months after a single intravenous dose of ^{131}I -MIBG: 808 mCi (13 mCi/kg). ULN: upper limit of normal.

with tumor. Such marrow involvement is a relative contraindication to PBSC leukapheresis, although exceptions can be made if marrow involvement is limited.

Patient Evaluation and Preparation for High-Dose ^{131}I -MIBG Therapy

Prospective subjects for this Phase II clinical trial were carefully evaluated in preparation for ^{131}I -MIBG therapy, as detailed in TABLE 1. Patients with hypertension are treated with antihypertensive medications as described above. Menstruating women received one intramuscular injection of sustained-release medroxyprogesterone acetate (Depo-Provera) 150 mg before high-dose ^{131}I -MIBG therapies in order to prevent menorrhagia during thrombocytopenia. Patients continue to receive their usual analgesics and other medications. However, all medications known to interfere with MIBG uptake are prohibited, particularly labetalol, tricyclics, phenothiazines, and decongestants.

^{131}I -MIBG Formulation

UCSF Nuclear Medicine obtains ^{131}I from commercial sources as a reactor product. Although a fission ^{131}I product is now available, most exchange labelings of ^{127}I -MIBG for therapy at UCSF have been with MDS Nordion's ^{131}I reactor product. On the morning of therapy, the UCSF nuclear pharmacist (J.P.H.) synthesizes the ^{131}I -MIBG by exchange-labeling 15 mCi (reactor)

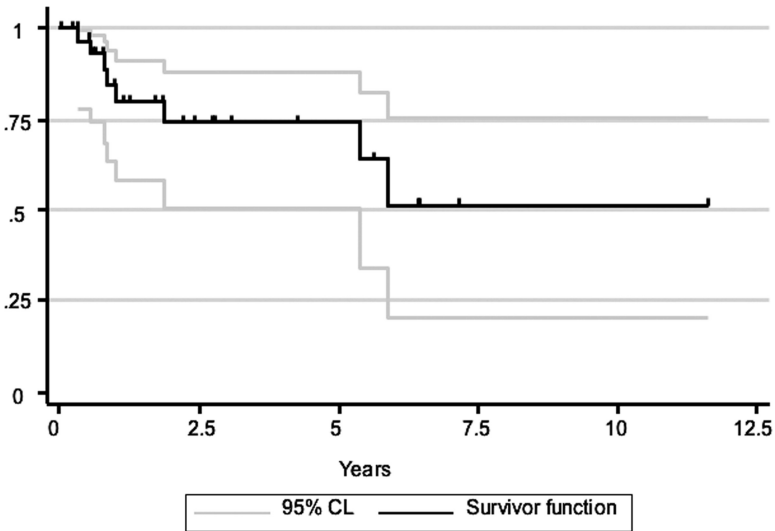


FIGURE 3. Standard Kaplan–Meier overall survival estimate with 95% confidence limits (CL) for 30 patients with metastatic paraganglioma or pheochromocytoma, from the time of ^{131}I -MIBG therapy. The survival estimate includes all-cause mortality, including two patients with non-tumoral mortality.

or 50 mCi (fission) ^{131}I /mmol ^{127}I -MIBG in a solid-phase Cu^{2+} -catalyzed exchange reaction.

All exchange labelings have been conducted using the solid-phase (ammonium sulfate) method with Cu^{2+} catalysis, typically incubating 600–1400 mCi ^{131}I with a much larger amount of ^{127}I -MIBG. (Molar ratio of approximately 1:1000) in a protected hot-cell designed for this purpose. On account of shielding constraints, hot-cell activities are limited to 2 Ci and room activity to 1500 mCi. The nuclear pharmacist delivers the ^{131}I -MIBG to the patient's room in a lead-shielded container.

This exchange-labeling process of synthesizing ^{131}I -MIBG yields a mixture of ^{131}I -MIBG and ^{127}I -MIBG in a molar ratio of about 1:1,000; this is known as “carrier added” ^{131}I -MIBG. About 97–98% of the radioactive isotope ^{131}I is bound to MIBG, leaving only about 2–3% free ^{131}I -MIBG; this is known as having a high “specific activity”.

UCSF Hospital Care During ^{131}I -MIBG Therapies

Patients are admitted to the University of California, San Francisco on Thursdays to lead-lined rooms that had been prepared in advance by UCSF Environmental Health and Safety. Adults are admitted to the oncology unit,

whereas children are admitted to UCSF Children's Hospital Pediatric Clinical Research Center.

All patients with hypertension were treated with antihypertensives. Nifedipine was used preferentially. Labetalol was not used, on account of its known inhibition of MIBG uptake into tumors.

On the evening of admission, all patients receive a bladder catheter; an intravenous line is established, and intravenous 0.9 normal saline solution is infused for the duration of the hospitalization. A second peripheral intravenous line is established with an angiocatheter, heparin-locked, and lightly taped in preparation for the ^{131}I -MIBG infusions.

For thyroid protection against free ^{131}I , all patients receive potassium iodide (KI) and potassium perchlorate (KClO_4). For nausea prophylaxis, patients are administered granisetron 2 mg orally daily for 5 to 7 days, beginning on the morning of the ^{131}I -MIBG infusions. In the event of vomiting, intravenous granisetron or ondansetron is used. For sedation or additional anti-emetic effect, lorazepam 1 mg was administered intravenously or orally every 6 to 8 hours.

For prophylaxis against deep vein thrombosis, all adult patients receive low molecular weight heparin (enoxaparin 40 mg) subcutaneously daily for the first 3 days of their hospitalization, while they have a bladder catheter and are at bed rest. The patients receive their usual medications, as long as they are not known to interfere with ^{131}I -MIBG uptake.

In preparation for the ^{131}I -MIBG infusion, each patient's bladder catheter is drained into a lead-lined container by the bedside, from which it is constantly pumped away into a continuously flushing toilet.

UCSF ^{131}I -MIBG Infusion Protocol and Dosing

Adult patients are gently sedated with lorazepam 1 mg intravenously immediately prior to the isotope infusion. ^{131}I -MIBG is infused intravenously over 120 min via a peripheral intravenous line. The isotope activity is pumped from a shielded vial through micropore tubing past an infrared bubble detector. Blood pressure and pulse are measured remotely every 15 min with an automated monitoring device during the isotope infusion. For systolic hypertension reaching 170 mm Hg, nifedipine 10 mg was administered orally. After the isotope infusion, the intravenous line used for the infusion is removed. A physician, nuclear pharmacist, and radiation safety specialist are present during each infusion of ^{131}I -MIBG.

The individual doses of ^{131}I -MIBG ranged from 557 mCi to 1185 mCi (mean 833 mCi). Expressed as mCi/kg body weight, the doses ranged from a low of 7.4 mCi/kg (large adult) to 18.75 mCi/kg (mean 12.6 mCi/kg).

Three days after the ^{131}I -MIBG infusion, the bladder catheter is typically removed. A laxative is administered to patients who are constipated. Four

days after the isotope infusion, a whole-body post-therapy scan is obtained. Most patients are discharged on their fifth to seventh day following the isotope infusion, as long as their γ radiation levels are below 7 mRem/h at 1 m for adults and 2 mRem/h for children. The patients whose γ radiation levels measuring 2–7 mRem/hr at 1 m are discharged with explicit radiation safety precautions.

Patient Evaluation After ^{131}I -MIBG Therapy

Following ^{131}I -MIBG therapy, patients receive a post-therapy scintigraphy scan prior to discharge, and then return home for close hematological surveillance and support. Patients are followed very carefully after high-dose ^{131}I -MIBG therapy as follows: CBC with absolute neutrophil counts twice weekly for at least 6 weeks and then every 3 months; thorough serum biochemistries once weekly for 6 weeks and then every 3 months; ^{131}I -MIBG whole-body scanning every 3–4 months; volumetric imaging of metastases with CT or MRI every 3–4 months; serum chromogranin A every 1 to 3 months; 24-h urine fractionated catecholamines and metanephrines every 3–4 months; serum TSH and thyroxine every 3 months. Pulmonary function testing was required for patients with pulmonary metastases. An echocardiogram was required for patients with cardiac avidity for ^{131}I -MIBG. A hematologist–oncologist follows all patients.

Myelosuppression After ^{131}I -MIBG: Patient Care

Aspirin is prohibited following high-dose ^{131}I -MIBG therapies because it inhibits platelet aggregation, an unwanted effect in view of expected thrombocytopenia. Patients developed myelosuppression, generally commencing about 2.5–3 weeks after ^{131}I -MIBG therapies. Thrombocytopenia usually appeared first and was treated with platelet transfusions for platelet counts less than 20,000/ μL at the discretion of the hematologist. After 30 initial ^{131}I -MIBG therapies, the grades of thrombocytopenia at nadir were: Grade 1 ($> 75,000/\mu\text{L}$) 4 patients; Grade 2 ($\geq 50,000/\mu\text{L}$ and $\leq 75,000/\mu\text{L}$) 2 patients; Grade 3 ($> 10,000/\mu\text{L}$ and $< 50,000/\mu\text{L}$) 21 patients; and Grade 4 ($\leq 10,000/\mu\text{L}$).

GCSF was empirically administered to patients with an absolute neutrophil count (ANC) below 500/ μL . Antibiotics (usually levofloxacin) were administered for fever or prophylactically to patients with an ANC below 200/ μL . Erythropoietin analogues are empirically given for significant anemia. Red blood cell transfusions were administered as clinically indicated. Infusion of autologous cryopreserved peripheral blood stem cells (PBSCs) were administered to four patients with an ANC $< 200/\mu\text{L}$, Hct $< 25\%$, or PLT

<20,000/ μ L (treatment-dependent for over 2 weeks). No patient developed irreversible myelosuppression after ^{131}I -MIBG therapies.

Non-hematological Adverse Reactions to High-Dose ^{131}I -MIBG

Most patients experienced varying degrees of nausea or anorexia, beginning the evening after the ^{131}I -MIBG infusions. The nausea is believed due to radiation sickness, aggravated by oral administration of KI and KClO_4 . The nausea was usually mild and transient. Patients with a heavy tumor burden tended to experience more prolonged anorexia and nausea that lasted up to 3–4 weeks, long after the isotope had dissipated by excretion or decay.

Many patients experienced transient thinning of scalp hair after high-dose ^{131}I -MIBG. Sialadenitis occurred in several patients whose parotid tenderness appeared to be subjectively relieved by sour lemon candies. Primary ovarian or testicular failure were documented in three patients who had received repeated doses of ^{131}I -MIBG and had extensive pelvic bone metastases.

Several patients have developed Graves' disease after MIBG therapy. One of these 30 patients developed Graves' disease 26 months after receiving ^{131}I -MIBG. Another patient, recently treated, developed Graves' disease 3 months after ^{131}I -MIBG. A child (treated at UCSF under the concurrent neuroblastoma ^{131}I -MIBG treatment protocol) also developed Graves' disease after ^{131}I -MIBG. Graves' disease may have been triggered by the large doses of KI that were administered for thyroid protection, with a mechanism akin to amiodarone-induced hyperthyroidism.

Many feared toxicities have *not* developed after high-dose ^{131}I -MIBG. The normal liver absorbs a large portion of the administered ^{131}I -MIBG by a cation transporter mechanism, and the liver shows significant uptake of ^{131}I -MIBG on the post therapy scans. Therefore, liver enzymes were monitored weekly in all patients for 6 weeks and then regularly thereafter. No patients developed hepatic toxicity after high-dose ^{131}I -MIBG therapies. Patients with numerous large hepatic metastases did not show any sign of liver toxicity, despite significant uptake of isotope into their hepatic metastases. The normal adrenal medulla takes up ^{131}I -MIBG, but no patients have developed primary adrenal insufficiency. The sympathetic nervous system has robust norepinephrine uptake-1 activity, but we have not observed adrenergic insufficiency in any patient. The heart can have significant uptake of ^{131}I -MIBG, but no therapy-related cardiac toxicity has been observed.

CONCLUSION

For patients with paraganglioma or pheochromocytoma metastases having good ^{131}I -MIBG uptake on diagnostic scanning, high-dose ^{131}I -MIBG therapy can be effective therapy. In our experience, 67% of patients had a sustained CR,

PR, or SD. The calculated 5-year survival was 75% from time of treatment. While there is some significant potential toxicity, this therapeutic approach is generally very well tolerated. The results from this ongoing Phase II study demonstrate the efficacy of high-dose ^{131}I -MIBG therapy for selected patients with malignant pheochromocytoma and paraganglioma. However, novel therapies are needed. We may be able to improve such patients' outcomes with refinements in ^{131}I -MIBG synthesis and dosing, and by developing techniques to improve these tumors' sensitivity to ^{131}I -MIBG as well as their uptake and retention of the isotope.

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REFERENCES

1. BEARD, C.M. *et al.* 1983. Occurrence of pheochromocytoma in Rochester, Minnesota, 1950 through 1979. *Mayo Clin. Proc.* **58**: 802–804.
2. STENSTROM, G. & K. SVARDSUDD. 1986. Pheochromocytoma in Sweden 1958–1981. An analysis of the National Cancer Registry Data. *Acta Med. Scand.* **220**: 225–232.
3. HARTLEY, L. & D. PERRY-KEENE. 1985. Phaeochromocytoma in Queensland: 1970–83. *Aust. N. Z. J. Surg.* **55**: 471–475.
4. ANDERSEN, G.S. *et al.* 1988. The incidence rate of phaeochromocytoma and Conn's syndrome in Denmark, 1977–1981. *J. Hum. Hypertens.* **2**: 187–189.
5. BAGUET, J.P. *et al.* 2004. Circumstances of discovery of phaeochromocytoma: a retrospective study of 41 consecutive patients. *Eur. J. Endocrinol.* **150**: 681–686.
6. SUTTON, M.G. *et al.* 1981. Prevalence of clinically unsuspected pheochromocytoma: review of a 50-year autopsy series. *Mayo Clin. Proc.* **56**: 354–360.
7. CIFTCI, A.O. *et al.* 2001. Pheochromocytoma in children. *J. Pediatr. Surg.* **36**: 447–452.
8. TANAKA, S. *et al.* 1993. Malignant pheochromocytoma with hepatic metastasis diagnosed 20 years after resection of the primary adrenal lesion. *Intern. Med.* **32**: 789–794.
9. LEHNERT, H. *et al.* 2004. Malignant pheochromocytoma. *In* Pheochromocytoma. Pathophysiology and Clinical Management. *Frontiers of Hormone Research*. Vol. 31, A.B. Grossman, Ed.: 155–162. S. Karger, Basel, Switzerland.
10. THOMPSON, L.D.R. 2002. Pheochromocytoma of the adrenal gland scaled score (PASS) to separate benign from malignant neoplasms. *Am. J. Surg. Pathol.* **26**: 551–556.

11. KIMURA, N. *et al.* 2005. Histological grading of adrenal and extra-adrenal pheochromocytomas and relationship to prognosis: a clinicopathological analysis of 116 adrenal pheochromocytomas and 30 extra-adrenal sympathetic paragangliomas including 38 malignant tumors. *Endocr. Pathol.* **16**: 23–32.
12. BROWN, H.M. *et al.* 1999. Predicting metastasis of pheochromocytomas using DNA flow cytometry and immunohistochemical markers of cell proliferation. *Cancer* **86**: 1583–1589.
13. SALMENKIVI, K. *et al.* 2001. Increased expression of cyclooxygenase-2 in malignant pheochromocytomas. *J. Clin. Endocrinol. Metab.* **86**: 5615–5619.
14. OISHI, S. & T. SATO. 1988. Elevated serum neuron-specific enolase in patients with malignant pheochromocytoma. *Cancer* **61**: 1167–1170.
15. RAO, F. *et al.* 2000. Malignant pheochromocytoma: chromaffin granule transmitters and response to treatment. *Hypertension* **36**: 1045–1052.
16. SHORT, J.H. & T.D. DARBY. 1967. Sympathetic nervous system blocking agents. III. Derivatives of benzylguanidine. *J. Med. Chem.* **10**: 833–840.
17. SISSON, J.C. *et al.* 1981. Scintigraphic localization of pheochromocytoma. *N. Engl. J. Med.* **305**: 12–17.
18. SHAPIRO, B. *et al.* 1984. The location of middle mediastinal pheochromocytomas. *J. Thoracic Cardiovasc. Surg.* **87**: 814–820.
19. SHAPIRO, B. *et al.* 1985. Iodine-131 metaiodobenzylguanidine for the locating of suspected pheochromocytoma: experience in 400 cases. *J. Nucl. Med.* **26**: 576–585.
20. HATTNER, R.S. *et al.* 1984. Scintigraphic detection of pheochromocytomas using m-iodo (I-131) benzylguanidine. *Noninvasive Med. Imaging* **1**: 105–109.
21. TSUCHIMACHI, S. *et al.* 1997. Metastatic pulmonary pheochromocytomas: positive I-123 MIBG imaging with negative I-131 MIBG and equivocal I-123 MIBG planar imaging. *Clin. Nucl. Med.* **22**: 687–690.
22. ARGIRIS, A. *et al.* 2003. PET scan assessment of chemotherapy response in metastatic paraganglioma. *Am. J. Clin. Oncol.* **26**: 563–566.
23. PACAK, K. *et al.* 2004. Functional imaging of endocrine tumors: role of positron emission tomography. *Endocr. Rev.* **25**: 569–580.
24. MUKHERJEE, J.J. *et al.* 1997. Pheochromocytoma: effect of nonionic contrast medium in CT on circulating catecholamine levels. *Radiology* **202**: 227–231.
25. ILIAS, I. & K. PACAK. 2004. Anatomical and functional imaging of metastatic pheochromocytoma. *Ann. N.Y. Acad. Sci.* **1018**: 495–504.
26. KHORRAM-MANESH, A. *et al.* 2004. Mortality associated with pheochromocytoma in a large Swedish cohort. *Eur. J. Surg. Oncol.* **30**: 556–559.
27. BRAVO, E.L. 2002. Pheochromocytoma: an approach to antihypertensive management. *Ann. N. Y. Acad. Sci.* **970**: 1–10.
28. SANTEIRO, M.L. *et al.* 1996. Phenoxylbenzamine placental transfer during the third trimester. *Ann. Pharmacother.* **30**: 1249–1251.
29. COMBEMALE, F. *et al.* 1998. Exclusive use of calcium channel blockers and cardioselective beta-blockers in the pre- and peri-operative management of pheochromocytomas. 70 cases. *Ann. Chir.* **52**: 341–345.
30. LEBUFFE, G. *et al.* 2005. The effect of calcium channel blockers on outcome following the surgical treatment of pheochromocytomas and paragangliomas. *Anaesthesia* **60**: 439–444.
31. BLAKE, G.M. *et al.* 1988. Modification by nifedipine of ¹³¹I-metaiodobenzylguanidine kinetics in malignant pheochromocytoma. *Eur. J. Nucl. Med.* **14**: 345–348.

32. MINAMI, T. *et al.* 2002. An effective use of magnesium sulfate for intraoperative management of laparoscopic adrenalectomy for pheochromocytoma in a pediatric patient. *Anesth. Analg.* **95**: 1243–1244.
33. KHAFAGI, F.A. *et al.* 1989. Labetalol reduces iodine-131 MIBG uptake by pheochromocytoma and normal tissues. *J. Nucl. Med.* **30**: 481–489.
34. STEINSAPIR, J. *et al.* 1997. Metyrosine and pheochromocytoma. *Arch. Intern. Med.* **157**: 901–906.
35. MUKHERJEE, J.J. *et al.* 1997. Pheochromocytoma: effect of nonionic contrast medium in CT on circulating catecholamine levels. *Radiology* **202**: 227–231.
36. DINER, E.K. *et al.* 2005. Partial adrenalectomy: The National Cancer Institute experience. *Urology* **66**: 19–23.
37. GUERRIERI, M. *et al.* 2005. Laparoscopic adrenalectomy in pheochromocytomas. *J. Endocrinol. Invest.* **28**: 523–527.
38. DAVIES, M.J. *et al.* 2004. A comparison of open and laparoscopic approaches to adrenalectomy in patients with phaeochromocytoma. *Anaesth. Intensive Care* **32**: 224–229.
39. ELDADAH, B.A. *et al.* 2004. Cardiac uptake-1 inhibition by high circulating norepinephrine levels in patients with pheochromocytoma. *Hypertension* **43**: 1227–1234.
40. AVERBUCH, S.D. *et al.* 1988. Malignant pheochromocytoma: effective treatment with a combination of cyclophosphamide, vincristine, and dacarbazine. *Ann. Intern. Med.* **109**: 267–273.
41. PATEL, S.R. *et al.* 1995. A 15-year experience with chemotherapy of patients with paraganglioma. *Cancer* **76**: 1476–1480.
42. KOSHIHARA, K. *et al.* 1989. Remarkable regression of malignant paraganglioma in the retroperitoneum and neck after chemotherapy: report of a case and a review of the literature. *Jpn. J. Med.* **28**: 772–776.
43. MICHAELSON, M.D. & M.R. SMITH. 2005. Bisphosphonates for treatment and prevention of bone metastases. *J. Clin. Oncol.* **23**: 8219–8224.
44. BRIEGER, J. *et al.* 2005. Vascular endothelial growth factor expression, vascularization and proliferation in paragangliomas. *ORL J. Otorhinolaryngol. Relat. Spec.* **67**: 119–124.
45. TONG, A.L. *et al.* 2004. [Expression of transforming growth factor alpha, tumor necrosis factor alpha, and vascular endothelial growth factor of human pheochromocytoma tissues]. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao.* **26**: 426–431.
46. TAKEKOSHI, K. *et al.* 2004. Expression of vascular endothelial growth factor (VEGF) and its cognate receptors in human pheochromocytomas. *Life Sci.* **74**: 863–871.
47. SALMENKIVI, K. *et al.* 2003. VEGF in 105 pheochromocytomas: enhanced expression correlates with malignant outcome. *APMIS.* **11**: 458–64.
48. GIMENEZ-ROQUEPLO, A.P. *et al.* 2002. Functional consequences of a SDHB gene mutation in an apparently sporadic pheochromocytoma. *J. Clin. Endocrinol. Metab.* **87**: 4771–4774.
49. MIDDEKE, M. *et al.* 2002. *In vitro* and *in vivo* angiogenesis in PC12 pheochromocytoma cells is mediated by vascular endothelial growth factor. *Exp. Clin. Endocrinol. Diabetes* **110**: 386–392.
50. ZIELKE, A. *et al.* 2002. VEGF-mediated angiogenesis of human pheochromocytomas is associated to malignancy and inhibited by anti-VEGF antibodies in experimental tumors. *Surgery* **132**: 1056–1063.

51. FERRARA, N. *et al.* 2004. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. *Nat. Rev. Drug Discovery* **3**: 391–400.
52. ZACHARIAH, A. & G. SCOFF. 2005. Update on angiogenesis inhibitors. *Curr. Opin. Oncol.* **17**: 578–583.
53. RYAN, A.J. & S.R. WEDGE. 2005. ZD6474—a novel inhibitor of VEGFR and EGFR tyrosine kinase activity. *Br. J. Cancer* **92**: S6–13.
54. HOLDEN, S.N. *et al.* 2005. Clinical evaluation of ZD6474, an orally active inhibitor of VEGF and EGF receptor signaling, in patients with solid, malignant tumors. *Ann. Oncol.* **16**: 1391–1397.
55. ZATELLI, M.C. *et al.* 2005. Cyclooxygenase-2 inhibitors reverse chemoresistance phenotype in medullary thyroid carcinoma by a permeability glycoprotein-mediated mechanism. *J. Clin. Endocrinol. Metab.* **90**: 5754–5760.
56. STARKOVA, A.M. *et al.* 1998. Nifedipine-induced morphological differentiation of rat pheochromocytoma cells. *Neuroscience* **86**: 611–617.
57. YU, L. *et al.* 1996. Radiation therapy of metastatic pheochromocytoma: case report and review of the literature. *Am. J. Clin. Oncol.* **19**: 389–393.
58. GERSZTEN, P.C. & W.C. WELCH. 2004. Cyberknife radiosurgery for metastatic spine tumors. *Neurosurg. Clin. N. Am.* **15**: 491–501.
59. SISSON, J.C. *et al.* 1984. Radiopharmaceutical treatment of malignant pheochromocytoma. *J. Nucl. Med.* **24**: 197–206.
60. CHARBONNEL, B. *et al.* 1988. Le traitement des pheochromocytomas malins par la 131-I-metaitodobenzylguanidine. *Ann. Endocrinol. (Paris)* **49**: 344–347.
61. BRENDDEL, A. *et al.* 1989. Radionuclide therapy of pheochromocytomas and neuroblastomas using Iodine-131-metaitodobenzylguanidine (MIGB). *Clin. Nucl. Med.* **14**: 19–21.
62. TRONCOME, L. *et al.* 1990. The diagnostic and therapeutic utility of radioidonated metaiodobenzylguanidine (MIBG): 5 years experience. *Europ. J. Nucl. Med.* **16**: 325–335.
63. LOH, K.C., P.A. FITZGERALD, *et al.* 1997. The treatment of malignant pheochromocytoma with Iodine-131 metaiodobenzylguanidine (¹³¹I-MIBG): a comprehensive review of 116 reported patients. *J. Endocrinol. Invest.* **20**: 648–658.
64. MUKHERJEE, J.J. *et al.* 2001. Treatment of metastatic carcinoid tumors, pheochromocytoma, paraganglioma and medullary carcinoma of the thyroid with ¹³¹I-meta-iodobenzylguanidine (¹³¹I-mIBG). *Clin. Endocrinol.* **55**: 47–60.
65. SAFFORD, S.D. *et al.* 2003. Iodine-131 metaiodobenzylguanidine is an effective treatment for malignant pheochromocytoma and paraganglioma. *Surgery* **134**: 956–963.
66. KORAL, K.F. *et al.* 1989. Calculating radiation absorbed dose for pheochromocytoma tumors in 131-I MIBG therapy. *Int. J. Radiat. Oncol. Bio. Phys.* **17**: 211–218.
67. MAIRS, R.J. *et al.* 1995. Enhanced tumour uptake and *in vitro* radiotoxicity of no-carrier-added ¹³¹I-metaiodobenzylguanidine: implications for targeted radiotherapy of neuroblastoma. *Eur. J. Cancer* **31**: 576–581.
68. MATTHAY, K.K. *et al.* 1998. Phase I dose escalation of ¹³¹I-metaiodobenzylguanidine with autologous bone marrow support in refractory neuroblastoma. *J. Clin. Oncol.* **16**: 229–236.
69. SUNG, K.W. *et al.* 2002. Double high-dose chemotherapy with autologous stem cell transplantation in patients with high-risk neuroblastoma: a pilot study in a single center. *J. Kor. Med. Sci.* **17**: 537–543.

70. CHOU, T. *et al.* 2005. Isolation and transplantation of highly purified autologous peripheral CD34+progenitor cells: purging efficacy, hematopoietic reconstitution following high dose chemotherapy in patients with breast cancer: results of a feasibility study in Japan. *Breast Cancer* **12**: 178–188.
71. ROSE, B. *et al.* 2003. High-dose ¹³¹I-Metaiodobenzylguanidine therapy for 12 patients with malignant pheochromocytoma. *Cancer* **98**: 1–10.
72. BENNETT, J.M. & R.S. KOMROKJI. 2005. The myelodysplastic syndromes: diagnosis, molecular biology and risk assessment. *Hematology* **10**: 258–269.
73. WEISS, B. *et al.* 2003. Secondary myelodysplastic syndrome and leukemia following ¹³¹I-metaiodobenzylguanidine therapy for relapsed neuroblastoma. *J. Pediatr. Hematol. Oncol.* **25**: 543–547.
74. GARAVENTA, A. *et al.* 2003. Second malignancies in children with neuroblastoma after combined treatment with ¹³¹I-metaiodobenzylguanidine. *Cancer* **97**: 1332–1338.