

# Malignant paraganglioma

Linda D. Bosserman, MD, FACP,<sup>1</sup> and Paul Fitzgerald, MD<sup>2</sup>

<sup>1</sup>Wilshire Oncology Medical Group, Inc., La Verne, CA, and

<sup>2</sup>University of California, San Francisco, School of Medicine, San Francisco, CA

A common problem in the practice of oncology and hematology is the patient with a rare malignancy, where the challenge to the clinician is to rapidly gain an understanding of the latest thinking and treatment approaches, determine how and where this care can be delivered, and then establish how to get that treatment plan paid for by insurance or other sources. As a recent case in point from their practices, the authors present the case history of a 43-year-old man with a metastatic paraganglioma. The case illustrates the myriad issues and challenges faced by the doctor, staff, patient, family, consulting experts, lawyers, and insurers in developing and implementing a complex treatment plan. The methods used to achieve a successful outcome for this patient are discussed, plus suggested newer approaches that might improve care for patients with this and other rare cancers.

## Case history

Linda D. Bosserman, MD, FACP

**P**atient GW was a 43-year-old engineer and married father of three who was in excellent health until May 2002 when he presented with progressive back pain of several months' duration. Work-up included an MRI of the lumbar spine showing marrow infiltration within the L3 and L4 vertebral bodies, invasion of the posterior half of L4 with a pathologic fracture, and 30% height loss in that vertebra, as well as a 15 × 13 cm intra-abdominal mass extending from the aorta to the anterior abdominal wall.

A computed tomographic (CT) scan of the chest showed no adenopathy or parenchymal disease. CT scan of the abdomen and pelvis confirmed the presence of a 13-cm intraperitoneal/mesenteric mass with central necrosis and no compression of retroperitoneal vascular structures. A bone scan showed numerous metastatic sites, with activity in the left innominate bone near S1, mid-sacrum on the right, T5, and L4, as well as the right frontoparietal calvaria, where he had a palpable scalp mass.

An ultrasound-guided biopsy of the abdominal mass revealed a malignant paraganglioma. Initial laboratory panel was normal—including catecholamine,

metanephrine, and vanillylmandelic acid (VMA) levels, but an elevated 24-hour dopamine level (656 mg/d; normal, 65–400 mg/d). During the several weeks of work-up, his scalp lesion rapidly expanded to a tender, 6-cm lesion. When the scalp lesion was biopsied to obtain a larger sample for diagnostic confirmation, tumor was also sent for chemosensitivity testing to Rational Therapeutics in Long Beach, CA, at the patient's expense. Beyond the recommended CVD (cyclophosphamide, vincristine, and dacarbazine) regimen, the literature was not directive in choosing chemotherapy with any of the many newer chemotherapeutic agents, if they became an option in the future. It was hoped that chemosensitivity testing might help guide future treatments if no other evidence-based data were available.

### Initial treatment

Treatment for immediate pain control was initiated in June 2002 with long- and short-acting opioids and irradiation to the thoracic and lumbar spine and, after biopsy, to the scalp lesion. This treatment resulted in rapid pain relief and local control of the scalp tumor, and we were able to taper the patient off of all opioids over several weeks.

Chemotherapy was initiated with CVD for two cycles in July and August

of 2002, with the goal of shrinking the abdominal tumor and preventing rapid growth while coordinating possible long-term remission approaches with medical experts and the patient's insurance carrier.

### Consultation

In August 2002, after two courses of CVD chemotherapy, restaging showed that there had been no significant shrinkage of tumor. Consultation was arranged with Dr. Paul Fitzgerald at the University of California, San Francisco, Medical Center (UCSF), an 8-hour drive from the patient's home. An initial <sup>123</sup>I-MIBG (iodine-123 metaiodobenzylguanidine) scan at UCSF on August 21, 2002, showed uptake in the main 14 × 16 cm abdominal tumor, as well as in the scalp tumor, mid-sternum, posterior right rib, left lateral pelvic rim, L4, and right sacrum. Pathology slides were reviewed at UCSF, and the diagnosis of malignant paraganglioma was confirmed. The chromogranin A (CgA) level was found to be markedly elevated at 1,840 ng/mL (normal, 6–39 ng/mL).

Correspondence to: Linda D. Bosserman, MD, FACP, Wilshire Oncology Medical Group, Inc., 1502 Arrow Highway, La Verne, CA 91750; telephone: (909) 593-4333; e-mail: linda.bosserman@womgi.com

Commun Oncol 2004;1:47–52  
© 2004 BioLink Communications, Inc.

A multimodality, evidence-based treatment plan was developed under the expert direction of Dr. Fitzgerald and coordinated by myself as the local oncologist for the patient's managed care plan for available in-plan services, at UCLA (University of California at Los Angeles, the usual tertiary center for this patient's managed health care plan) and with UCSF.

### Surgery

Surgical treatment at UCLA, an hour's drive from the patient's home, was arranged after several delays, letters of medical necessity, and personal phone calls from me, as well as from the patient and his wife. On September 10, 2002, the patient underwent surgery by the chief of oncologic surgery, Dr. James Economou, and his colleagues at UCLA, who used their years of clinical expertise to successfully remove the patient's abdominal tumor, which was adherent to the aorta and inferior vena cava. Surgery was supported by 12 U packed red blood cells, 10 U fresh fro-

zen plasma, 10 U cryoprecipitate, and 10 U platelets.

Concomitant with his surgery, GW underwent stem-cell harvesting by Dr. Ronald Paquet of UCLA's hematology/oncology division for future use as needed with planned <sup>131</sup>I-MIBG therapy. The patient had a remarkable and rapid recovery from surgery and was hospitalized for *only* 7 days due to the expert medical care he received. The postoperative CgA level was 35 ng/mL.

### Further therapy

Then, in December 2002, after 3 months of health-plan delays, GW returned to Dr. Fitzgerald at UCSF for follow-up. His CgA level was now 13.3 ng/mL. After receiving 655 mCi of <sup>131</sup>I-MIBG on December 6, the patient returned to work full time and, over the next 16 weeks, was followed by me in his home town with careful laboratory monitoring for possible blood count suppressions that were not clinically symptomatic. Further <sup>131</sup>I-MIBG treatments were anticipated.

A follow-up diagnostic <sup>123</sup>I-MIBG

scan in February 2003 showed resolution of activity in all areas except for a rim of enhancement around the cranial lesion, which was of questionable significance. The CgA level was 35.4 ng/mL in February and had fallen to a normal value of 5.9 ng/mL by April 2003. A follow-up scan on July 23 again showed no activity except at the rim of the cranial lesion, which remained unchanged from the previous scan. Another follow-up scan on November 5, 2003, also showed no changes. The CgA level in October remained normal at 8.7 ng/mL.

As of March 2004, almost 2 years after the initial diagnosis, GW remains vigorously healthy without evidence of disease, working full time and enjoying being a father and husband. He will remain on an every-3-month follow-up schedule until year 2 after treatment and will then be seen every 6 months until 5 years after treatment. Retreatment with <sup>131</sup>I-MIBG is planned for any recurrence that is sensitive. For everyone involved, this outcome is a triumph of cooperative, modern medical care.

### *Malignant paraganglioma*

## Issues raised by this case

Paul Fitzgerald, MD

**P**aragangliomas are neuroendocrine tumors that arise from sympathetic nerve ganglia. They can develop anywhere from the neck (chemodectomas) to the pelvis but are most commonly found in the abdomen, particularly at the aortic bifurcation or in the peri-aortic region. Paragangliomas are histologically identical to pheochromocytomas that arise from the adrenal medulla. Malignancy is more common in paragangliomas (30%–50%) than in pheochromocytomas (10%–15%), with local invasion, destruction of adjacent vertebrae, and distant metastases to lungs, lymph nodes, and bones.

Patients with metastatic paragan-

glioma have been reported to have a median survival of about 4.5 years; however, indolent disease does occur, and prolonged survival has been reported. Malignancy must be distinguished from peritoneal seeding of tumor that can occur spontaneously or during the resection of a retroperitoneal paraganglioma, yielding multiple intra-abdominal tumors (pheochromocytomatosis) that rarely metastasize beyond the abdomen.

Familial paraganglioma is caused by a germline mutation in one of the genes encoding succinate dehydrogenase (SDHB, SDHC, or SDHD). In this condition, multiple paragangliomas can arise in the same individual

and must be distinguished from metastatic disease, which may coexist. Paragangliomas and pheochromocytomas occur at an early age in 20% of patients with von Hippel-Lindau (VHL) disease, and such tumors may be malignant.

### Diagnostic and localization studies

Between 36% and 60% of paragangliomas are functional and secrete norepinephrine and normetanephrine. Such patients may be hypertensive or normotensive. Paragangliomas do not ordinarily secrete epinephrine and are less likely to cause the severe symptom complex seen in patients with pheochromocytomas.

The lack of epinephrine secretion by paragangliomas is due to the fact that they are distant from the adrenal cortex and do not have the high local concentra-

tions of cortisol required to stimulate the expression of 4-phenylethanolamine-N-methyltransferase (PNMT), which catalyzes the conversion of norepinephrine to epinephrine in the adrenal medulla and adrenal pheochromocytomas. Patients' 24-hour urine collections are assayed for fractionated catecholamines, metanephrines, and creatinine. Most paragangliomas secrete chromogranin A (CgA), and serum CgA levels serve as a useful tumor marker that correlates with tumor burden.

The best localizing study for malignant paraganglioma is  $^{123}\text{I}$ -MIBG scanning with SPECT (single photon emission computed tomography); this can be combined with CT scanning to yield a "fusion" scan. Unfortunately, at least 30% of malignant paragangliomas do not concentrate MIBG. Other useful whole-body scanning modalities include  $^{111}\text{In}$ -octreotide scanning and positron emission tomography (PET) scanning using either  $^{18}\text{F}$ -deoxyglucose ( $^{18}\text{F}$ -FDG) or  $^{18}\text{F}$ -dopamine. MRI scanning is particularly useful for visualizing abdominal and bone tumors. CT scanning is most useful for visualizing lung and abdominal tumors. The intravenous (IV) contrast medium used in CT scanning may provoke a hypertensive crisis in patients with paragangliomas that secrete norepinephrine; IV contrast media should not be used in such patients unless they are prepared beforehand with alpha-adrenergic blockers and are closely monitored throughout the procedure.

## Treatment of malignant paraganglioma

### *Surgery*

Following appropriate treatment of hypertension with alpha-adrenergic blockade and calcium-channel blockers, surgical resection of the primary tumor is recommended. Surgery can be technically difficult for these vascular tumors, particularly when they

involve the heart, aorta, vena cava, kidneys, or bladder. A team approach is often required for successful surgery, and close hemodynamic monitoring during surgery is mandatory. Even in the presence of distant metastases, it is best to resect or debulk the primary tumor whenever possible. Skull metastases can often be resected, with cranioplasty when indicated.

### *$^{131}\text{I}$ -MIBG*

High-dose  $^{131}\text{I}$ -MIBG was first used to treat malignant pheochromocytomas in 1983 at the University of Michigan. Like sympathetic synapses, pheochromocytomas and paragangliomas are usually avid for norepinephrine. Benzylguanidine resembles norepinephrine, and iodine 131 is tagged to it, producing  $^{131}\text{I}$ -MIBG, a targeted radionuclide. As the iodine 131 decays, it releases local high-energy beta particles that damage or destroy the tumor cell; concomitant release of gamma rays allows post-therapy whole-body scanning. In order to deliver a therapeutic dose to the tumors, a large amount of  $^{131}\text{I}$ -MIBG must be administered to the patient.

Although  $^{131}\text{I}$ -MIBG is readily available in doses used for diagnostic scanning (eg, 5 mCi), it is not commercially available in the large amounts required for a treatment (500–800 mCi). Such high doses of  $^{131}\text{I}$ -MIBG must be synthesized on site at the treating medical center; this requires special licensing of the facility, an experienced nuclear pharmacist, and a "hot cell" for its preparation. High-dose  $^{131}\text{I}$ -MIBG therapy must be done with stringent radiation precautions, and the patient must remain quarantined in a lead-shielded room for about 5 days or until radiation emissions have declined to a level safe enough for the patient to be discharged.  $^{131}\text{I}$ -MIBG therapy is available at the UCSF Medical Center under a phase II study protocol with the approval of the UCSF Committee on Human Research, the UCSF Comprehensive Cancer Center, and

the UCSF Pediatric Clinical Research Center.

High-dose  $^{131}\text{I}$ -MIBG therapy has been moderately successful in treating patients with malignant paraganglioma or pheochromocytoma whose tumors are avid for the isotope. Following  $^{131}\text{I}$ -MIBG therapy, the majority of such patients experience a partial remission and stabilization of disease. When treated with very high doses of  $^{131}\text{I}$ -MIBG, 3 of 12 such patients have experienced complete remissions.

Bone marrow suppression is the main side effect of high-dose  $^{131}\text{I}$ -MIBG therapy. The majority of patients require transfusions and marrow support for low blood counts, which occur about 3 weeks after therapy. Pancytopenia is usually transient, but stem-cell harvest has been obtained prior to therapy for all patients who are to receive  $^{131}\text{I}$ -MIBG doses over 12 mCi/kg or who have already received chemotherapy or external radiation therapy to bones.

### *External radiation therapy*

Radiation therapy is useful for treating patients with painful bone metastases. However, irradiated tumors lose their avidity for  $^{131}\text{I}$ -MIBG. Therefore, external radiation therapy ideally should be administered after  $^{131}\text{I}$ -MIBG therapy to patients who remain symptomatic. External radiation therapy should not be administered to treat intra-abdominal paragangliomas, due to its side effects and lack of effectiveness.

### *Chemotherapy*

Combined use of cyclophosphamide, vincristine, and dacarbazine (CVD) appears to be the most effective chemotherapeutic regimen for patients with metastatic paraganglioma or pheochromocytoma. However, complete long-term remissions have not occurred with any chemotherapy regimen, and multiple cycles of CVD chemotherapy must be administered chronically every 21 days.

*Malignant paraganglioma*

## Information on the care of rare cancers and health plan coverage issues

Linda D. Bosserman, MD, FACP

**A**s a community oncologist facing a very rare cancer diagnosis, I first went to the Internet for guidance, using my standard sources of Medscape ([www.medscape.com](http://www.medscape.com)) and PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>). Medscape, going back 70 months, led to four articles on biliary paraganglioma, one of which had some good background information. PubMed brought up 13,485 articles under malignant paraganglioma. Adding review criteria to the search still brought up 1,789 articles, many of which were on pheochromocytoma. Other articles were on paragangliomas of the nasal cavity, posterior mediastinum, urinary bladder, and parasellar region. Finally, I found three articles dealing with the abdominal/adrenal area: one by a Swedish group; a report of <sup>131</sup>I-MIBG therapy from Durham, NC; and a report on CVD chemotherapy response from a Japanese group.

Searching UpToDate.com (<http://uptodate.com>), which I have found very helpful to gain quick, comprehensive reviews of cancer issues and to which I have a subscription, revealed information on paragangliomas in the pheochromocytoma section but little detail about abdominal tumors. Their one comment on <sup>131</sup>I-MIBG was, "In initial studies, local tumor irradiation with <sup>131</sup>I-MIBG has proven to be of limited therapeutic value." They also mentioned that CVD chemotherapy was effective, but not curative, for aggressive tumors.

I spent more than 12 hours on the Internet searching for information, reading articles, and trying to understand how to craft a combined modality treatment plan to give this patient a reasonable chance at controlling his

disease for as long as possible, all the time realizing that, with aggressive, distant metastatic disease, the likelihood of cure was remote. From my reading, even a year of control seemed questionable. I did not find any local experts to call for consultation.

### Call to an academic colleague

Next, I called Dr. Peter Rosen at UCLA, who is admired by community doctors near and far for his photographic memory and unfailing good humor, and who can be counted on to return your phone calls. I described the case to him and the results of my searches, after which, in his usual collegial manner, he proceeded to tell me he had treated several of these patients in collaboration with Dr. Paul Fitzgerald at UCSF, who was a world expert on this disease...and also easy to work with.

Dr. Rosen mentioned that in previous cases they had harvested stem cells for use with multiple <sup>131</sup>I-MIBG doses over time, and that the UCLA team might be able to resect the abdominal tumor for debulking; he also suggested that we could coordinate the <sup>131</sup>I-MIBG treatments at UCSF under a protocol by Dr. Fitzgerald. Although we realized that the chances of long-term benefits were low, a multidisciplinary treatment plan began to shape up.

I started the CVD chemotherapy while arranging the multitude of consultations and authorizations needed to get this patient evaluated and treated with the most likely effective therapy for this extremely rare and aggressive cancer.

### Referrals to UCLA

UCLA is the preferred tertiary center for the managed healthcare

plan to which this patient belonged. Consultations were requested, with detailed rationales in the dictated consultation notes provided for the hematology and surgical oncology consultations. The health plan initially referred the surgery back to an in-plan surgeon, who, fortunately, was an excellent clinician and had had some surgical oncology training. On discussing the case with him, he agreed that if resection of such an involved tumor was possible, it would best be done at UCLA.

For the hematology consult, several explanations were needed, because stem-cell harvesting is not a recognized procedure for postradiation treatment support; thus, coverage was initially denied. Once consultations were finally authorized and made, all agreed to re-evaluate the patient after the ongoing chemotherapy was completed. Unfortunately, when the post-chemotherapy assessment was done, it showed no response of the disease. A proposal was then formulated for resective surgery and concomitant stem-cell harvesting at UCLA, because it was likely that follow-up therapy with <sup>131</sup>I-MIBG would be effective for residual disease. This coverage request was finally submitted in September 2002.

### Referral to UCSF and Dr. Fitzgerald

After many meetings, phone calls, and letters of medical necessity, consultation with Dr. Fitzgerald and preliminary MIBG scanning were authorized. That scan showed diffuse uptake, which meant that the tumor would be amenable to therapeutic <sup>131</sup>I-MIBG after debulking surgery and stem-cell harvesting, per the <sup>131</sup>I-MIBG protocol. The treating team agreed that the surgery and stem-cell harvesting could be done at UCLA, where the health plan had a regular referral contract and which was close to the patient's home. The surgery and stem-cell harvesting would be followed with <sup>131</sup>I-MIBG therapy at UCSF, where a protocol was in place for patients with these types

of MIBG-sensitive cancers to receive treatment with  $^{131}\text{I}$ -MIBG, which is in very limited supply and, when available, needs to be used within a short time frame.

Unfortunately, major problems were encountered in getting authorization for the postsurgical scan and  $^{131}\text{I}$ -MIBG treatment. The local independent practice association (IPA) deferred authorization to the health plan. At the health plan level, the treatments were denied, and further letters of medical necessity from both Dr. Fitzgerald and myself were requested and provided. Treatment was still denied as experimental and lacking safety data. The patient, with the support of the doctors, made further health plan appeals, but these, too, were denied.

### Retaining expert legal counsel

These denials and delays led the family to hire a well-respected local attorney, Paul Mahoney, of Jones, Mahoney, Brayton and Soll, Claremont, CA, who became active in helping them address their legal rights to obtain the care recommended by the specialist physician team, but in support of which there was limited literature due to the rarity of the cancer. Significant uncompensated time was spent on these issues by all parties involved, but, nevertheless, there was a significant delay in instituting the planned  $^{131}\text{I}$ -MIBG therapy, as the family could not pay for its significant cost.

The treatment request was finally submitted by the health plan to a three-physician review panel for final arbitration, as required by state law. The panel consisted of a medical oncologist, surgical oncologist, and radiation oncologist, all of whom admitted in detailed written reports that they had no experience with such tumors. The vote was two to one in favor of the health plan denying coverage of the  $^{131}\text{I}$ -MIBG therapy, on the grounds of inadequate safety data and the experimental nature of the therapy. Letters were sent to the

patient and each of the doctors, informing them of this non-appealable final decision to deny coverage.

The cost of the planned  $^{131}\text{I}$ -MIBG treatment was estimated as follows: stem-cell harvest stimulated with granulocyte colony-stimulating factor (filgrastim [Neupogen]) is about \$3,500, plus an additional \$3,000 if an additional leukapheresis session is required. The cost of obtaining 1,000 mCi of iodine 131, its synthesis into approximately 800 mCi  $^{131}\text{I}$ -MIBG, and delivery of  $^{131}\text{I}$ -MIBG to the patient adds up to a nuclear medicine cost of about \$10,000–\$12,000. In addition, the total costs for 6–7 days of hospitalization run about \$28,000–\$30,000.

Patients require close surveillance after therapy, requiring twice-weekly

laboratory testing for about 6 weeks. About 60% of patients require one to four platelet transfusions, filgrastim, and/or epoetin alfa (Epogen, Procrit). About 10%–20% of patients have required reinfusion of stem cells. The net cost for the first  $^{131}\text{I}$ -MIBG treatment runs about \$50,000, and the patient would probably require multiple doses over time. However, negotiated cost incurred by insurers can be up to 30% less. Despite arguments that patients in California have the right to coverage for clinical trials of treatments that are likely to be of benefit for their disease, this treatment was still denied.

### The Attorney General's office gets involved

Fortunately, the expert legal assistance of Mr. Mahoney and complaints

## The attorney's view

Paul M. Mahoney, Attorney at Law  
Jones, Mahoney, Brayton & Soll, LLP, Claremont, CA

OUR OFFICE GOT INVOLVED IN GW'S case in October 2002, when it appeared that the health plan would not authorize Dr. Fitzgerald's recommended treatment based on an independent medical review panel. After a series of letters and direct dialogue between the health plan's counsel and myself, I was able to persuade the health plan to conduct an additional independent medical review through a review organization known as Hayes Plus, in Lansdale, PA.

Hayes Plus asked for additional information from Dr. Fitzgerald, who readily complied. One week later, in November 2002, I received a call from the health plan's lawyer indicating that GW would be allowed to undergo the treatment with Dr. Fitzgerald. I then coordinated contact with Dr. Fitzgerald's office and at UCLA regarding the harvesting of GW's stem cells.

In March 2003, it appeared that there was going to be an interruption of coverage previously approved, but once I sent another letter to the health plan's attorneys, that issue was resolved, and GW's treatment continued uninterrupted.

Had coverage been denied, we were prepared to file suit, without charge, on GW's behalf in Federal Court to try to get a federal judge to approve the treatment, since GW's health plan was covered under ERISA. I dealt on an almost daily basis directly with the health plan's attorney, and our firm was ready to file suit on 4 hours' notice if the second appeal before Hayes Plus had not been favorable.

In the end, the health plan saw the light, without the need for litigation to do the right thing, and GW got the right treatment and is now doing fine. Unfortunately, this isn't a common result in healthcare litigation.

to the Department of Managed Care by the patient's wife also led to the involvement of an attorney from the California Attorney General's office, who called me to discuss the case. I was most impressed with his understanding of California law about clinical trials coverage and his ability to sort out issues. We discussed that, although this treatment was being given as part of a carefully designed protocol with informed consent,  $^{131}\text{I}$ -MIBG was not considered an experimental drug, so it was not being paid for under the clinical trial program. This was a key point cited in the health plan denial. In fact, in this case,  $^{131}\text{I}$ -MIBG was the only reasonably effective medical therapy available for this rare disease.

After our discussion, the attorney from the Attorney General's office called the health plan's medical director to advocate for their covering the  $^{131}\text{I}$ -MIBG therapy as being "the most reasonable medical therapy for his disease" and not because it was part of a clinical trial.

Meanwhile, using this same argument, Mr. Mahoney had continued his diligent efforts on behalf of GW. He and the physicians made another appeal to the health plan, which was, thankfully, finally approved. Without the expert legal help of Mr. Mahoney, this treatment would not have been possible unless the family mortgaged their home to pay for the treatment.

### How we need to improve the future for patients with rare cancers

This case illustrates several steps that could be taken to ensure that patients with rare diseases get medically necessary treatment, even if it is not considered "standard of care" but, rather, the only reasonable treatment plan likely to benefit their disease in a timely and efficient manner. Specific areas of need include:

- *Rapid access to highly specialized consultations.* Designing and initiating

a website that would contain a list of experts in various rare cancers would make this information rapidly available to treating physicians. It would allow physicians to quickly contact experts and develop treatment plans for these complex patients.

In addition, the Internet and the availability of centralized protocol review processes provide excellent resources for expert panels to propose the best course of therapy for patients with rare diseases, including the list of experts both close by and distant. Publication of treatment results from even small series of patients would be a tremendous improvement over current literature, which often consists of only single case reports with varying treatment approaches.

- *Rapid access to health plan treatment decision makers.* The "standard of care" for patients with rare diseases is often a work in progress because of lack of data, including information on new drugs that might be promising. Doctors need rapid access to decision makers in the health plan who can cut through the many approval layers, letters, denials, and phone calls from doctors, patients, and their desperate families, all anxious to initiate the most likely effective therapy while it has the best chance of improving patient outcomes. The development of such a complex, multi-institutional plan, as was needed for this patient, is so protracted and time consuming that most doctors in private practice and their staffs would be unable to contribute to a successful outcome.

Oncology organizations need to work together with health plans to develop a framework methodology that could approve individual treatment plans for these challenging patients.

- *Adjusted criteria for clinical trial participation and off-label drug use.* Since the most medically reasonable treatment with the greatest likelihood of benefit should be determined in the setting of a clinical trial protocol, so that all of the data are collected

for later publication to benefit others with such rare diseases, treatment on such protocols needs to be covered by insurance.

Moreover, given the rare nature of these cancers, it is incumbent upon medical oncologists to call for the development of procedures to ensure that patients who, in good faith, buy health insurance are covered for medically necessary costs, even when data are lacking due to the rarity of their diagnosis. When using available agents "off label," the health plans should agree to cover such costs. In these cases, flexibility with regard to covering the cost of judicious use of assays that can help guide chemotherapy choices is appropriate. Oncology organizations need to discuss these issues with health plans and work toward specific legislation, if necessary.

### Suggested reading

1. Averbuch SD, Steakley CS, Young RC, et al. Malignant pheochromocytoma: effective treatment with a combination of cyclophosphamide, vincristine, and dacarbazine. *Ann Intern Med* 1988;109:267-273.
2. Loh KC, Fitzgerald PA, Matthay KK, et al. The treatment of malignant pheochromocytoma with iodine-131 metaiodobenzylguanidine ( $^{131}\text{I}$ -MIBG): a comprehensive review of 116 reported patients. *J Endocrinol Invest* 1997;20:648-658.
3. Roman S. Pheochromocytoma and functional paraganglioma. *Curr Opin Oncol* 2004;16:8-12.
4. Rose B, Matthay KK, Price D, et al. High-dose  $^{131}\text{I}$ -metaiodobenzylguanidine therapy for 12 patients with malignant pheochromocytoma. *Cancer* 2003;98:239-248.
5. Safford SD, Coleman RE, Gockerman JP, et al. Iodine-131 metaiodobenzylguanidine is an effective treatment for malignant pheochromocytoma and paraganglioma. *Surgery* 2003;134:956-962.

### ABOUT THE AUTHORS

Dr. Bosserman is Medical Oncologist and President of Wilshire Oncology Medical Group, Inc., La Verne, CA; Dr. Fitzgerald is Clinical Professor of Medicine and Attending Physician at the University of California, San Francisco, School of Medicine, where he is principal investigator for a phase II study of high-dose  $^{131}\text{I}$ -MIBG therapy for malignant pheochromocytoma and paraganglioma.