Changing Paradigms in the Treatment of Malignant Pheochromocytoma

Raymon H. Grogan, MD, Elliot J. Mitmaker, MD, and Quan-Yang Duh, MD

Background: Pheochromocytomas and paragangliomas are intra- and extra-adrenal neoplasms that are rarely malignant. The treatment of those that are malignant has remained a challenge because little was known about the molecular pathways involved in its malignant transformation. Recently, however, the genetic and molecular changes involved in malignant pheochromocytoma have come to be understood.

Methods: The authors review the recent literature about the changing treatment options for malignant pheochromocytomas and paragangliomas.

Results: Traditional treatments for malignant pheochromocytoma remain unsuccessful. With the advances made in genomics and proteomics, novel pathways in pheochromocytoma carcinogenesis are becoming the targets of new treatment strategies and show promising results.

Conclusions: Although several studies and clinical trials show great promise for improving the treatment of pheochromocytomas and paragangliomas, the hope is that future collaborative efforts will allow for prospective clinical trials using an evidenced-based approach.

Introduction

Paragangliomas are tumors of sympathetic and parasympathetic paraganglia cells. Pheochromocytomas are a specific type of paraganglioma that originate in the adrenal medulla. According to the 2004 World Health Organization definition, a pheochromocytoma is an endocrine tumor that originates in catecholamine-producing chromaffin cells of the adrenal medulla. Paragangliomas can arise in many different parts of the body, but they are classified by anatomic location into intra-adrenal and extra-adrenal sites. Extra-adrenal paragangliomas are further classified into four subgroups: branchiomeriac, intravagal, aorticosympathetic, and visceral-autonomic. This is an important distinction because the majority of head and neck paragangliomas are of parasympathetic origin and do not secrete catecholamines. Catecholamine status has important implications for the management and treatment of these tumors.

Historically, the treatment of malignant pheochromocytoma has been challenging. There is no cure, so treatment currently focuses on alleviating symptoms. Traditional anticancer treatments have been mostly ineffective, and studying outcomes of new forms of treatment has been difficult because the low prevalence of malignant disease makes it difficult to assemble adequately sized study cohorts. Further complicating this is a lack of consensus on how to distinguish benign from malignant pheochromocytoma, as well as a lack of understanding genetic and molecular changes involved in malignant pheochromocytoma are targets of novel treatment approaches.
on how these tumors develop. However, recent findings have advanced our understanding of the genetic and molecular causes of pheochromocytoma, which is leading to the development of new therapies. Standard therapies for malignant pheochromocytoma are mostly nonspecific therapies that indiscriminately target dividing cells. The newer therapies being developed are targeted therapies based on the molecular mechanisms involved in the formation of malignant pheochromocytoma. This is a change in our thinking and our approach to these cancers, which has been possible only since the molecular mechanisms of formation of malignant pheochromocytoma have come to be understood. This article reviews the changing paradigms in the treatment of malignant pheochromocytoma based on this new molecular and genetic evidence. The focus is on tumors of sympathetic origin.

### Malignant Pheochromocytoma

Unlike most tumors, no molecular or cellular markers identify a pheochromocytoma as malignant. Vascular invasion, cellular atypia, and even local recurrence do not definitively identify a pheochromocytoma as malignant. Currently, a malignant pheochromocytoma is defined only by the presence of metastasis.² The World Health Organization tumor classification suggests that between 3% and 13% of all pheochromocytomas are malignant.² Researchers from the Mayo Clinic found that pheochromocytomas occur in roughly 10 per 1,000,000 people.³ In the United States in 2002, the incidence of malignant pheochromocytoma was 93 cases in 400 million people.⁴ These statistics correspond with the World Health Organization’s data and suggest that in the United States, approximately 10% of all pheochromocytomas are malignant.² When considering both intra- and extra-adrenal paragangliomas, the malignancy rate increases from 13% to 36%.⁵ Extra-adrenal paragangliomas are more commonly malignant than intra-adrenal paragangliomas. The wider range of malignancy rates reported in the literature may also be the result of a nonstandardized definition of malignancy has been used in the past. The 5-year survival rate for malignant disease is estimated to be between 34% and 60%, depending on the location of metastasis. Patients with bone metastasis survive the longest, and those with lung and liver metastasis have the shortest life expectancies.⁵

Surgery is the main treatment for both benign and malignant pheochromocytoma. For malignant disease, a regimen of resection and debulking is recommended to reduce the tumor burden and symptoms of catecholamine excess, but recurrence rates are high. Treatment with iodine-131-meta-iodobenzylguanidine (I¹³¹-MIBG) is the most successful adjunct to surgical treatment and has shown some ability to cure in a small number of patients. Systemic chemotherapy is the second most useful adjunct, but its effects are mostly limited to short-term symptomatic relief, with recurrence rates of almost 100%. External beam radiation is used for treatment of head and neck paragangliomas of parasympathetic origin. It has been largely ineffective in treating metastatic pheochromocytomas or paragangliomas of sympathetic origin. For these tumors, external beam radiation is most beneficial for the treatment of metastasis to the bone. Experience with radiofrequency ablation for these cancers is minimal.

### Genetics of Pheochromocytoma

Most pheochromocytomas are sporadic tumors, but roughly 24% develop from hereditary germline mutations.⁶ Mutations of six different genes are known to cause hereditary pheochromocytomas and paragangliomas: the von Hippel-Lindau gene (VHL), the RET proto-oncogene, the neurofibromatosis type 1 gene (NF1), the succinate dehydrogenase B subunit gene (SDHB), the succinate dehydrogenase D subunit gene (SDHD), and the KIF1BBeta gene (Table 1).⁶⁻¹¹ Recent evidence has shown that these mutations are part of two distinct molecular pathways.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Exon</th>
<th>Protein</th>
<th>Germline Mutation Rate (%)</th>
<th>Malignancy Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VHL⁶⁻⁸</td>
<td>3p25-26</td>
<td>3</td>
<td>pVHL19 and pVHL30</td>
<td>2⁻¹¹</td>
<td>5</td>
</tr>
<tr>
<td>SDHB⁶⁻⁷</td>
<td>1p36.13</td>
<td>8</td>
<td>Catalytic iron-sulfur protein</td>
<td>3⁻¹⁰</td>
<td>50</td>
</tr>
<tr>
<td>SDHD⁴⁻⁷,⁹,¹⁰</td>
<td>11q23</td>
<td>4</td>
<td>CybS (membrane-spanning subunit)</td>
<td>4⁻⁷</td>
<td>&lt; 3</td>
</tr>
<tr>
<td>RET⁶⁻⁷</td>
<td>10q11.2</td>
<td>21</td>
<td>Tyrosine-kinase receptor</td>
<td>&lt; 5</td>
<td>3</td>
</tr>
<tr>
<td>NF1¹⁰</td>
<td>17q11.2</td>
<td>59</td>
<td>Neurofibromin</td>
<td>Unknown</td>
<td>11</td>
</tr>
<tr>
<td>KIF1BBeta</td>
<td>1p36.2</td>
<td>41</td>
<td>Kinesin family member 1B (microtubule motor)</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Mutations of \textit{VHL}, \textit{SDHB}, and \textit{SDHD} cause errors in the HIF hypoxia-driven transcription pathway (Figure), and mutations of \textit{RET} and \textit{NF1} cause errors in RNA synthesis and metabolism through the MAPK pathway. \textit{KIF1BBeta} is a more recently discovered mutation. Its pathway is not completely elucidated but seems to be connected to both the HIF and MAPK pathway.\textsuperscript{12} Gene expression profiles from tumors with these mutations show a predictable gene expression signature that can reliably predict the type of mutation causing the tumor formation.

HIF is a transcription factor responsible for regulating the cellular response to hypoxia. HIF is constitutively expressed and regulated by the oxygen tension in a cell. Under normoxic conditions, an ubiquitination process that is dependent on VHL continually degrades the HIF protein.\textsuperscript{13} Under hypoxic conditions, HIF is no longer degraded, and the protein stabilizes and begins to build up in the cell (Figure). Stable HIF then acts as a transcription factor that causes the upregulation of several genes involved in the hypoxia response. Many of these genes, such as vascular endothelial growth factor (VEGF), are responsible for angiogenesis as well as cellular growth and metabolism. HIF dysfunction has been implicated in many types of human tumors. It is thought that, in the adrenal gland, mutations of SDHB and SDHD cause tumor formation through the buildup of succinate. High levels of succinate interfere with the VHL-mediated degradation of HIF by preventing prolyl hydroxylases from hydroxylating HIF, which is a key step in the VHL process. Mutations of \textit{VHL}, \textit{SDHB}, and \textit{SDHD} lead to abnormal HIF activation, causing overexpression of angiogenesis factors and tumor formation (Figure).\textsuperscript{14}

The second set of related mutations cause abnormal expression of genes involved in RNA synthesis, protein production, and kinase signaling.\textsuperscript{14} It remains unclear exactly how these mutations cause the abnormal gene expression profiles that lead to tumor formation. However, \textit{RET}, \textit{NF1}, and \textit{KIF1BBeta} all participate in the molecular cascade that leads to apoptosis. Mutations of these genes are thought to decrease apoptosis, leading to abnormal cell growth. \textit{RET} and \textit{NF1} have both been shown to activate the MAPK pathway of cellular signaling via abnormal \textit{RAS} activation. Abnormal \textit{RAS} protein signaling has been implicated in a wide variety of human tumors.

The recent improved understanding of the molecular pathways that cause malignant pheochromocytoma formation is leading to the development of new drug therapies. These designer drugs are targeted at disrupting the abnormal cell signaling that is created by these mutations. While none is currently in clinical use, many are now being studied in clinical trials.

\textbf{\textit{I}^{31}MIBG Radiation Therapy}  
MIBG is structurally similar to noradrenaline. This causes its uptake and concentration into chromaffin cells, making it useful as an imaging tool for pheochromocytomas and paragangliomas of sympathetic origin. In 1984, investigators at the University of Michigan realized that this property of specific uptake by pheochromocytomas could make it a useful therapeutic tool as well.\textsuperscript{15,16} Ra-

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{Three HIF pathway mutations are associated with pheochromocytoma. The HIF protein regulates cellular responses to oxygen tension by acting as a transcriptional regulator for multiple proangiogenic factors. Under normal normoxic conditions, HIF is hydroxylated by PHDs allowing it to be degraded by a VHL-mediated process (left). Mutations of VHL prevent HIF degradation, causing increased HIF accumulation, unregulated angiogenesis, and tumor formation (middle). Mutations of SDHB and SDHD genes cause succinate to accumulate. Excess succinate prevents PHDs from hydroxylating HIF, which also leads to HIF accumulation, activation, and tumor formation. Under normal hypoxic conditions HIF is activated via the PHD pathway to promote angiogenesis (right). VHL = von Hippel-Lindau, PHD = prolyl hydroxylase domain, HIF = hypoxia-inducible factor, SDHB = succinate dehydrogenase B subunit gene, SDHD = succinate dehydrogenase D subunit gene.}
\end{figure}
dioactive iodine (I\textsuperscript{131}), known to be effective in treating thyroid cancer, was attached to the MBG molecule to produce I\textsuperscript{131}-MBG, which at high enough doses could then be used as a semi-selective radiation therapy agent for malignant pheochromocytoma. The fact that it must be taken up specifically by the cells of the tumor is also one of its drawbacks. Some malignant pheochromocytomas do not take up MBG, and in these tumors, I\textsuperscript{131} MBG therapy is useless. External beam radiation therapy abolishes the ability of these tumors to take up MBG, making this treatment ineffective in any tumor that has been irradiated.\textsuperscript{17}

Since 1984, many case reports have demonstrated the utility of I\textsuperscript{131}-MBG radiation therapy for treating symptomatic disease, and a few cases of complete responses have been published. A retrospective review of 116 patients showed a tumor response in 30%, a biochemical response in 45%, and symptomatic relief in 76%.\textsuperscript{18} Another recent retrospective review of 19 patients showed an objective tumor response in 47%, a biochemical response rate of 67%, and temporary symptomatic relief in 89%.\textsuperscript{19} That study also reported a hematologic complication rate in 26%. A phase II clinical trial of high-dose I\textsuperscript{131}-MBG therapy in 30 patients showed a 67% tumor response rate and a 75% 5-year survival rate. Because high-dose I\textsuperscript{131}-MBG therapy is myeloablative, stem cells from peripheral blood must be obtained before treatment.\textsuperscript{20}

I\textsuperscript{131}-MBG therapy is the most widely studied nonsurgical therapy for malignant pheochromocytoma and is considered the most useful treatment for patients whose tumors are not resectable. Many case reports have been published on the use of I\textsuperscript{131}-MBG therapy; with only a few large case series and one prospective controlled trial.\textsuperscript{18,20} Consequently, evidence-based assumptions about the utility of this therapy are problematic. Clearly, I\textsuperscript{131}-MBG therapy is not curative, but some evidence suggests a high-dose regimen can result in sustained complete remission in a small number of patients. Its high side effect profile at higher doses and low improvement in overall survival make it less than ideal, but it remains the best nonsurgical option to date.

### Chemotherapy

Many different types of systemic chemotherapy for malignant pheochromocytoma have been tried, with varying degrees of success. One of the most difficult aspects of understanding the utility of chemotherapy for malignant pheochromocytoma is that few prospective trials have investigated different types of chemotherapy options (Table 2).\textsuperscript{21-25} Instead, most knowledge about the effectiveness of chemotherapy is based on anecdotal evidence and single patient experiences.\textsuperscript{26} In a 1988 study that remains one of the largest series published on chemotherapy for malignant pheochromocytoma, 14 patients from the National Institutes of Health (NIH) were treated in a trial of combined cyclophosphamide, vincristine, and dacarbazine (CVD therapy).\textsuperscript{25} This regimen was chosen because of its high rate of success in treating neuroblastoma. Because neuroblastoma and pheochromocytoma are both neuroendocrine tumors, the thinking was that CVD therapy might be effective for pheochromocytoma. The NIH updated the study with an additional 4 patients in a 22-year follow-up analysis.\textsuperscript{22} In the trial, 55% of the tumors had a positive response to the treatment by decreased size criteria and 72% of the tumors had a biochemical response. The median duration of the response was 20 months. The trial also showed that biochemical markers — 24-hour urine catecholamines, metanephrines, and vanillylmandelic acid — are useful for determining tumor response, relapse, and progression. Based on this trial, which is the largest trial to date, CVD therapy resulted in no statistically significant survival advantage. It remains useful for controlling symptoms of catecholamine excess in at least 50% of patients who have unresectable disease. Because 55% of tumors had a significant reduction in size after treatment, CVD may be beneficial in select cases as a neoadjuvant therapy to improve the chances of surgical resection in large tumors, but no study has addressed this specifically.\textsuperscript{22} Patients being treated with CVD therapy need antihypertensive blockade beforehand because the therapy can cause a hypertensive crisis secondary to catecholamine release during treatment.
Another combination chemotherapy regimen (cyclophosphamide, doxorubicin, and dacarbazine) showed a tumor response rate of 46%,24 which was somewhat lower than that for CVD therapy. Other regimens that have been tested in smaller numbers of patients include (1) cisplatin and 5-fluorouracil, (2) etoposide, carboplatin, vincristine, cyclophosphamide, and doxorubicin, (3) CVD with anthracycline, (4) cyclophosphamide and methotrexate, (5) temozolomide, and (6) streptozocin with varying combinations of other agents.22,27 Most of these regimens have been shown to be either ineffective or effective in so few patients that no evidence-based conclusions can be drawn about their utility for treating malignant pheochromocytoma.

In summary, CVD therapy is the most widely used systemic chemotherapy regimen for malignant pheochromocytoma. Its use is mostly reserved for patients with unresectable disease who are symptomatic from catecholamine excess and had no response to 131I-MIBG therapy. However, because CVD therapy has no proven survival benefit, it should not be routinely administered to all patients with metastatic disease. It may have some role as a neoadjuvant therapy. The tumor typically recurs once the chemotherapy regimen is stopped, and once the tumor recurs, it may become unresponsive to that same regimen.22 Because any chemotherapy for malignant pheochromocytoma needs to be given long-term, it has to be considered on a case-by-case basis.

Radiation Therapy and Radiofrequency Ablation

Many case reports but few large patient series or controlled trials have been published on the use of radiation for malignant pheochromocytoma. A seminal review of the literature in 1978 concluded that radiation therapy is not useful as a primary mode of therapy and does not prevent local recurrence.26 Its main benefit is for controlling symptoms and pain associated with bone and lymph node metastasis. Since then, additional case reports have shown radiation therapy to be somewhat useful for bone metastasis, but generally, a malignant pheochromocytoma is thought to be a radiation-resistant tumor.28 Cyberknife radiation therapy delivers external radiation in a focused manner, allowing for much higher doses to be given with fewer side effects to the surrounding normal tissue.29 No studies have specifically investigated the use of cyberknife for a malignant pheochromocytoma, but cyberknife is a well-established method of treating bone metastasis of other tumor types, and it likely has a role in treating bone metastasis in malignant pheochromocytoma.

Little information is available on the use of radiofrequency ablation of metastatic pheochromocytoma lesions.30 A recent case series of seven tumors describes successful ablation of the tumor tissue in all but one case, although follow-up data were not available to determine the response rate and possible recurrence of the tumors.31 Data from adrenocortical carcinoma suggest that radiofrequency ablation of tumors within the adrenal gland is safe, but no data are available on the efficacy of this procedure for pheochromocytomas.32 More experience with radiofrequency ablation of malignant pheochromocytoma is needed to determine its usefulness in treating these cancers.

Experimental and Targeted Therapies

The discoveries of molecular pathways and genetic mutations that characterize malignant pheochromocytomas and paragangliomas have greatly enhanced the ability to design specific anticancer therapies. Most of these therapies have cytostatic properties in that they not only kill cancer cells, but also can interfere with the cytotoxic activity of other chemotherapeutic drugs. In addition, they can modulate the activity of key enzymes responsible for the specific signaling pathways capable of transforming benign pheochromocytomas and paragangliomas to their malignant counterparts. The cytostatic properties of these anticancer therapies are derived from the specific molecular targets found along the oncogenic signaling pathways that promote carcinogenesis and tumor growth.27 Specific receptors and proteins have been discovered and reflect the different genetic “clusters” that categorize the malignant transformation of these adrenal neoplasms. With the help of bioinformatics systems, high throughput genomics and proteomics have been instrumental in defining some of the mutations that subsequently lead to the development of several targeted therapies for the treatment of malignant pheochromocytomas and paragangliomas.

Therapeutic Targets

Heat Shock Protein 90 (Hsp90) — This multi-chaperone ATP-dependent complex is responsible for folding therapeutically relevant proteins, and it plays an important role in the stability and function of a host of oncoproteins (BCR-ABL, ERBB2, EGFR, CRAF, BRAF, AKT, MET, VEGFR, FLT3, AR, ER, HIF, and telomerase).33 These oncoproteins are responsible for many molecular processes usually attributed to the malignant phenotype, including growth factor independence, resistance to antigrowth signals, cell replication, tumor invasion and metastases, angiogenesis, and lack of apoptosis.34 Hsp90 may represent a potential therapeutic target as high levels of Hsp90 protein expression have been found in malignant compared to benign pheochromocytomas.35 Because of the many oncogenic signaling pathways regulated by Hsp90, inhibitors of Hsp90 can target several oncogenic proteins in parallel.34,36 Currently, no known drug trials are using Hsp90 inhibitors specifically against malignant pheochromocytomas or paragangliomas.

mTOR Inhibitors — The PI3K/AKT/mTOR pathway is responsible for regulating cell growth and survival.
If this pathway becomes dysfunctional, mTOR becomes upregulated, leading to increased cell proliferation, angiogenesis, and evasion of apoptosis. The mTOR inhibitor everolimus (RAD001) in combination with octreotide has been shown to be effective for low- and intermediate-grade neuroendocrine tumors. Most patients experienced either a partial response or stable disease, with a minority experiencing tumor progression. Along with this study, in vivo and in vitro experiments demonstrated a possible link between increased activity in the AKT pathway and the development of adrenal pheochromocytomas. However, while case series have shown that everolimus is not effective in treating patients with malignant pheochromocytoma because all patients experienced disease progression, the above-mentioned patients had aggressive disease with distant metastases, which likely influenced the outcomes of the study. Further studies on the PI3K/AKT/mTOR pathway may still be needed to determine a more specific molecular target along its path.

**HIF Inhibitors** — HIF is a key regulator of the tumor environment and has spawned the research and development of several targeted therapies. Some agents being investigated are PX-12 (1-methylpropyl 2-imidazolyl disulfide) and PX-478 (S-2-amino-3-[4′-N,N,N-bis (2-chloroethyl)amino]-phenyl propionic acid N-oxide dihydrochloride). HIF activity is decreased indirectly by PX-12 and is directly inhibited by PX-478. Although no data have been reported for malignant pheochromocytomas and paragangliomas, these agents have shown marked antitumor activity in various human tumor xenografts in mice. Studies are still required to determine the potential use of these new therapeutic targets.

**Prolyl Hydroxylase Activators** — Recent evidence has now indicated that activators of prolyl hydroxylase, such as R59949 and KRH102053, result in increased hydroxylation of HIF, which ultimately decreases the expression of proteins that regulate angiogenesis and those that resist apoptosis (Figure). As our understanding of the association between the HIF pathway and the role of prolyl hydroxylases in pheochromocytomas continues to expand, it is likely to lead to the discovery of new antineoplastic agents.

**ERBB2 (HER-2/neu) Inhibitors** — ERBB2 is a receptor tyrosine kinase involved in cell growth and differentiation. When activated, ERBB2 leads to the synthesis of HIF which subsequently leads to the overexpression of VEGF. The presence of ERBB2 overexpression is associated with an increase in tumor metastasis and resistance to cancer treatment. ERBB2 was significantly overexpressed in malignant pheochromocytomas compared to benign or extra-adrenal pheochromocytomas. Although ERBB2 may be overexpressed, this does not necessarily imply that it would serve as a useful therapeutic target, as seen by the HER-2/neu oncogene and the response of targeted therapies in breast cancer. To date, there have been no published trials using ERBB2 (HER-2/neu) inhibitors for patients diagnosed with malignant pheochromocytomas. Clinical trials assessing the efficacy of trastuzumab (Herceptin) may be on the horizon.

**Specific Therapies**

**Thalidomide** — Initially introduced in the 1950s as a sedative, thalidomide was quickly removed from the market when its teratogenic effects became known. At the turn of this century, thalidomide, in combination with dexamethasone, gained popularity when it was shown to increase survival in patients diagnosed with multiple myeloma. Thalidomide is an antiangiogenic agent, specifically targeting VEGF and basic fibroblast growth factor (bFGF). Several phase III trials are studying the effects of thalidomide in metastatic renal cell cancer, multiple myeloma, and non-small cell lung cancer. To date, only one phase II trial has been conducted to determine potential therapeutic efficacy.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Molecular Target</th>
<th>Potential Targeted Therapy</th>
<th>Trial Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kulke et al54</td>
<td>Vascular endothelial growth factor (VEGF)</td>
<td>Thalidomide</td>
<td>I/II</td>
</tr>
<tr>
<td>Kulke et al54</td>
<td>Basic fibroblast growth factor (bFGF)</td>
<td>Thalidomide</td>
<td>I/II</td>
</tr>
<tr>
<td>Gross et al56</td>
<td>Receptor tyrosine kinase (RTK): KIT, PDGF-R, and ABL</td>
<td>Imatinib mesylate</td>
<td>I/II</td>
</tr>
<tr>
<td>Joshua et al58</td>
<td>VEGF, PDGFR-β, c-KIT, FLT3, and RET</td>
<td>Sunitinib</td>
<td>I/II</td>
</tr>
<tr>
<td>Jimenez et al59</td>
<td>Mammalian target of rapamycin (mTOR)</td>
<td>Everolimus (RAD001)</td>
<td>I/II</td>
</tr>
<tr>
<td>Yao et al58</td>
<td>Hypoxia-inducible factor 1-alpha (HIF-1α)</td>
<td>PX-478</td>
<td>N/A</td>
</tr>
<tr>
<td>Druce et al53</td>
<td>PX-12</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Welsh et al55,56</td>
<td>Prolyl hydroxylase</td>
<td>KRH102053</td>
<td>N/A</td>
</tr>
<tr>
<td>Choi et al61</td>
<td>ERBB-2 (HER-2/neu)</td>
<td>Trastuzumab</td>
<td>N/A</td>
</tr>
<tr>
<td>Temes et al48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saeger et al61</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
termine the efficacy of thalidomide in combination with temozolomide, a cytotoxic chemotherapeutic agent, as an alternative to streptozocin-based therapy in neuroendocrine tumors. In the pheochromocytoma group, which included 3 patients, a partial radiologic response to the therapy occurred in 1 patient. Due to the limited number of cases, it is impossible to draw any conclusions about the efficacy of thalidomide in pheochromocytoma patients. However, the combination of thalidomide and temozolomide may offer some benefit to pheochromocytoma patients in addition to patients with carcinoid and/or pancreatic neuroendocrine tumors.54

**Imatinib Mesylate** — This tyrosine kinase inhibitor specifically inhibits the protein tyrosine kinase activity of the BCL-ABL, c-KIT, and PDGF-R enzymes. Imatinib, as a targeted therapy against the BCL-ABL gene and the tyrosine kinase protein c-KIT, became important as an effective treatment for hematologic malignancies (eg, chronic myelogenous leukemia) as well as solid tumors (eg, gastrointestinal stromal tumors). Several studies were designed to determine whether other solid endocrine malignancies expressed either PDGF-R or c-KIT. Yet, the data for patients with malignant pheochromocytomas (n = 2) indicated progression of disease. Interestingly, the immunohistochemical profiles of these tumors (PDGF-R+ and c-KIT+; PDGF-R+ and c-KIT−) made no difference in the tumors’ response to imatinib.56

**Sunitinib** — Sunitinib is a receptor tyrosine kinase inhibitor that acts on several targets (VEGF, PDGF-c-KIT) and demonstrates antiangiogenic and antitumor activity. The mechanism by which sunitinib acts on malignant pheochromocytomas and paragangliomas is associated with the mutation of the VHL gene. The VHL gene, as previously mentioned, leads to the activation of HIF and

<table>
<thead>
<tr>
<th>NCT ID</th>
<th>Trial Description</th>
<th>Study Type and Design</th>
<th>Trial Phase</th>
<th>Recruitment (mm/yyyy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00923481</td>
<td>To study R935788 (fostamatinib disodium), a multikinase inhibitor that interferes with cell communication and growth of malignant cells in pheochromocytoma</td>
<td>Interventional; treatment, nonrandomized</td>
<td>II</td>
<td>03/2009</td>
</tr>
<tr>
<td>NCT00843037</td>
<td>To study the efficacy and toxicity profile of sunitinib malate in patients with recurrent pheochromocytoma/paraganglioma</td>
<td>Interventional; treatment, nonrandomized</td>
<td>II</td>
<td>02/2009</td>
</tr>
<tr>
<td>NCT00874614</td>
<td>To study the efficacy and safety of Ultratrace iobenguane I131 in treating patients with recurrent or refractory malignant pheochromocytoma/paraganglioma</td>
<td>Interventional; treatment, nonrandomized</td>
<td>II</td>
<td>06/2009</td>
</tr>
<tr>
<td>NCT00339131</td>
<td>To study the safety of Ultratrace iobenguane I131 in patients with malignant pheochromocytoma/paraganglioma</td>
<td>Interventional; treatment, nonrandomized</td>
<td>I</td>
<td>06/2006 (completed)</td>
</tr>
<tr>
<td>NCT00458952</td>
<td>To determine whether iobenguane (MIBG) I131 is safe and effective in malignant pheochromocytoma/paraganglioma</td>
<td>Interventional; treatment, nonrandomized</td>
<td>I and II</td>
<td>04/2007 (active, not recruiting)</td>
</tr>
<tr>
<td>NCT00107289</td>
<td>To determine the response of iodine I131 metaiodobenzylguanidine in patients with recurrent, progressive or refractory malignant pheochromocytoma/paraganglioma</td>
<td>Interventional; treatment</td>
<td>II</td>
<td>05/2006</td>
</tr>
<tr>
<td>NCT00049023</td>
<td>To evaluate the safety and tolerability of radiolabeled (90Y-DOTA-tyr3)-octreotide in children with refractory somatostatin-receptor positive tumors</td>
<td>Interventional; treatment</td>
<td>I</td>
<td>01/2002</td>
</tr>
<tr>
<td>NCT00002947</td>
<td>To determine the safety, toxicity profile and preliminary antitumor activity of indium In111 pentetreotide in patients with refractory malignancies expressing somatostatin receptors</td>
<td>Interventional; treatment</td>
<td>I</td>
<td>10/1996 (active, not recruiting)</td>
</tr>
<tr>
<td>NCT00655655</td>
<td>To study the side effect profile and best dose of the mTOR inhibitor RAD001 (everolimus) when given in combination with the VEGF receptor tyrosine kinase inhibitor PTK787/ZK (Vatalanib)</td>
<td>Interventional; treatment</td>
<td>I</td>
<td>12/2004 (active, not recruiting)</td>
</tr>
<tr>
<td>NCT00843531</td>
<td>To study the safety and efficacy of RAD001 plus erlotinib in patients with well to moderately differentiated neuroendocrine tumors</td>
<td>Interventional; treatment</td>
<td>II</td>
<td>06/2009</td>
</tr>
<tr>
<td>NCT00028106</td>
<td>To study the effectiveness of I131-metaiodobenzylguanidine (MIBG) in the treatment of malignant pheochromocytoma</td>
<td>Interventional; treatment</td>
<td>II</td>
<td>12/2001 (completed)</td>
</tr>
<tr>
<td>NCT00002608</td>
<td>To study the efficacy of combination chemotherapy (cisplatin and doxorubicin) given with tamoxifen in the treatment of endocrine malignancies</td>
<td>Interventional; treatment</td>
<td>II</td>
<td>05/1994 (completed)</td>
</tr>
</tbody>
</table>

Information based on clinical trials listing on clinicaltrials.gov (search terms: pheochromocytoma and/or paraganglioma).

NCT ID = National Clinical Trials Identifier
upregulates both VEGF and PDGF. Sunitinib can inhibit both the VEGF and PDGF receptors, as was previously shown in renal cell malignancies.59 Case studies have reported partial or near-complete tumor regression after treatment with sunitinib by measuring tumor size, performance status, patient symptoms, and reduction of biochemical tumor marker (normetanephrines and chromogranin A) levels.58,60 The preliminary results of the effectiveness of sunitinib as a molecular-targeted therapy for malignant pheochromocytomas and paragangliomas are promising. Phase II trials are currently underway (Table 3).58,43,45-48,54,56,58,60,61

**Clinical Trials**

Several phase I and II clinical trials are currently recruiting patients who have been diagnosed with either malignant or refractory pheochromocytomas and paragangliomas or with other metastatic neuroendocrine tumors expressing somatostatin receptors. The spectrum of trials ranges from the discovery of novel diagnostic assays for pheochromocytomas/paragangliomas to novel targeted therapeutic agents and newly radiolabeled somatostatin analogs for the treatment of these malignant tumors. Table 4 lists the clinical trials that are recruiting new patients. If successful, the new agents being studied in these trials might improve the treatment of malignant pheochromocytomas and paragangliomas.

**Conclusions**

No effective cure currently exists for patients diagnosed with malignant pheochromocytomas and paragangliomas. Until now, no histopathologic markers could be used to distinguish between a benign and malignant pheochromocytoma. However, over the past several decades, advances in bioinformatics and molecular biology have provided the impetus for the discovery of new diagnostic and prognostic tests, better imaging techniques, and improvements in chemotherapy, radiation therapy, and therapeutic regimens that use nuclear medicine technology. With the help of genomic and proteomic studies, novel tumor markers are currently being discovered and the paths of malignant transformation are now better defined. Despite these improvements, limitations still exist. Malignant pheochromocytomas and paragangliomas are rare cancers, and ambiguity persists for physicians and surgeons in terms of the available treatment strategies. Although several studies show promising results, development of an evidence-based approach is essential. The future of research for these tumors lies in the development of patient registries, international tissue bank programs, and collaborative prospective clinical trials for the treatment of these rare malignancies.

**References**