THERAPY OF ENDOCRINE DISEASE

Treatment of malignant pheochromocytoma and paraganglioma

Eric Baudin, Mouhammed Amir Habra1, Frederic Deschamps, Gilbert Cote1, Frederic Dumont, Maria Cabanillas1, J Arfi-Roufe, A Berdelou, Bryan Moon1, Abir Al Ghuzlan, Shreyaskumar Patel1, Sophie Leboulleux and Camilo Jimenez1,†

Département de Médecine Nucléaire et de Cancérologie Endocrinienne, Radiologie Interventionnelle, Chirurgie, Imagerie, Institut Gustave Roussy, Université Paris Sud, 114 Rue Edouard Vaillant 94805 Villejuif Cedex, Paris, France and 1Department of Endocrine Neoplasia and Hormone Disorders, Unit 1461, The University of Texas MD Anderson Cancer Center, 1400 Pressler Street, Houston, Texas 77030, USA

†(C Jimenez is now at The University of Texas MD Anderson Cancer Center, 1400 Pressler Street Unit 1461, Houston, Texas 77004, USA)

Correspondence should be addressed to E Baudin or C Jimenez
Email baudin@igr.fr or cjmenez@mdanderson.org

Abstract

Metastatic pheochromocytomas and paragangliomas (MPPs) present clinicians with three major challenges: scarcity, complexity of characterization, and heterogeneous behavior and prognosis. As with the treatment for all neuroendocrine tumors, the control of hormonal symptoms and tumor growth is the main therapeutic objective in MPP patients. A significant number of MPP patients still die from uncontrolled hormone secretion. In addition, the management of MPPs remains palliative. Steps forward include proper characterization of MPP patients at large cancer referral centers with multidisciplinary teams; improved strategies to stratify patients prognostically; and implementation of trials within national and international networks. Progress in the molecular characterization and staging of MPPs constitutes the basis for significant treatment breakthroughs.

Introduction

Malignant pheochromocytomas and paragangliomas (MPPs) constitute a subgroup of neuroendocrine tumors (NETs) defined by the presence of chromaffin tissues in extra-adrenal or paraganglion sites. Because they are NETs, MPPs are defined by their endocrine tumor morphology and positive immunohistochemical staining for chromogranin A and synaptophysin; negative staining for keratins allows MPPs to be differentiated from the metastases of gastrointestinal NETs (1). The diagnosis of MPPs is made either at the time of first evaluation by thorough radiographic evaluation and/or surgical exploration or over long-term follow-up lasting months, years, or even decades. The presence of clinical predictors of metastases and overall survival, such as the size, location (adrenal or extra-adrenal),
and genotype of the primary tumor, can help clinicians determine the required radiographic studies to assess disease extension at the time of the discovery of the primary tumor and during the long-term follow-up (2). Thus, patients with pheochromocytomas larger than 5 cm, paragangliomas of any size, and/or carriers of SDHB mutations need radiographic studies that can detect metastases in the thoracic, abdominal, and pelvic cavities and the skeletal tissue or recurrences in the primary tumor bed (2).

The incidence of MPPs is <1 per 1 million people/year. Approximately 10–20% of pheochromocytomas and paragangliomas are malignant. Malignancy is much more common in sympathetic paragangliomas than in pheochromocytomas, the incidence of which is higher (2). Owing to the low incidence of MPPs, few prospective studies have investigated potential therapies for the disease. Thus, advances in the understanding and management of MPPs largely depend on retrospective studies’ findings, expert consensus, and clinicians’ experience with other NETs. The implementation of networks for researching MPPs, such as the European Network for the Study of Adrenal Tumors and the Pheochromocytoma and Paraganglioma Research Support Organization, is a major step forward in the treatment of the disease. This review focuses on the therapeutic management of adult patients with MPPs.

**Characterization before therapy**

MPPs must be precisely characterized according to standardized criteria before therapy because this standardized characterization not only affects the therapeutic management of the disease, including the decision to treat, but also constitutes a modality for improving the understanding of a very rare cancer, the research of which is expected to primarily involve retrospective studies for many years. The minimum information that should be included in all MPP patients’ records is given in Table 1.

Advances in genetics and imaging studies have revealed that, compared with other diseases, MPPs lack validated prognostic indicators and therapies. The most robust studies of the characterization of MPP patients at the time of the diagnosis have suggested that metastatic adrenal and extra-adrenal tumors occur at equal rates and that the survival rates of metastatic adrenal and extra-adrenal tumors overlap (2); ~60% of MPP patients have tumor burden- and hormone-related manifestations (e.g., pain, hypertension, and constipation) (3); most MPPs produce noradrenaline and normetanephrine and/or dopamine and methoxytyramine, which partly reflects the higher risk of malignancy associated with SDHB mutations and extra-adrenal locations (4, 5, 6, 7, 8); most MPP patients have apparently sporadic tumors or tumors associated with germline or somatic mutations of the succinate dehydrogenase subunit B (SDHB) gene (2, 9, 10). The high prevalence of SDHB mutations (30–50% of patients) supports the screening of all patients with MPPs for such mutations.

Progress in imaging is remarkable. 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) is the most sensitive scintigraphic method for assessing MPPs (11). In addition, scintigraphy with 123I-metaiodobenzylguanidine (MIBG) can be used to determine whether patients are candidates for targeted radiotherapy with 131I-MIBG (12, 13). All foci of uptake should be correlated with guided conventional review or imaging. Computed tomography with optimal i.v. administration of contrast material has a high sensitivity (90–95%) for detecting primary tumors and metastatic and extra-adrenal lesions larger than 1 cm. The usual sites of metastatic involvement include the lymph nodes (80% of patients), bones (71%), liver (50%), and

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**Table 1** Minimum information to record at the presentation of patients with malignant pheochromocytomas and paragangliomas.

<table>
<thead>
<tr>
<th>Age and gender</th>
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</thead>
<tbody>
<tr>
<td>Performance status and comorbidities</td>
</tr>
<tr>
<td>Primary tumor location (If multiple tumors are present, the tumor that is &gt;5 cm and/or associated with local spread or regional positive lymph nodes is considered the primary tumor.)</td>
</tr>
<tr>
<td>Hormone- and tumor-related symptoms, including hypertension, constipation, and pain</td>
</tr>
<tr>
<td>Serum chromogranin A levels and urinary and/or plasma metanephrine, normetanephrine, and methoxytyramine levels indexed to urinary creatinine levels</td>
</tr>
<tr>
<td>Genetic syndrome</td>
</tr>
<tr>
<td>Best scintigraphic imaging among 18F-fluorodeoxyglucose positron emission tomography, metaiodobenzylguanidine scintigraphy, and somatostatin receptor scintigraphy</td>
</tr>
<tr>
<td>Bone, lung, liver, and lymph node tumor burden determined by head and neck, thoracic, abdominal, and pelvic computed tomography and/or magnetic resonance imaging in early arterial phase and guided computed tomography and/or magnetic resonance imaging</td>
</tr>
<tr>
<td>Morphological tumor progression at 3 months, without therapy if feasible</td>
</tr>
</tbody>
</table>

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lungs (50%) (8, 14, 15). Liver and bone magnetic resonance imaging, which may be more informative than computed tomography, is thus used for staging and follow-up (16, 17). Dedicated skeletal imaging to detect bone metastases (Fig. 1) and the clinical characterization of any bone metastases found are mandatory (15). In the absence of validated prognostic parameters, in asymptomatic patients with MPPs with no threatening masses, radiographic studies to assess disease progression should be conducted every 3 months for the first year. The results of these assessments will refine prognosis, the need and type of treatment (discussed in the following sections), and the follow-up modality of these patients (18).

In the characterization of MPPs, pathological differentiation and proliferative index have no prognostic value, which is in stark contrast to the characterization of other digestive and thoracic NETs. This indicates that pathological analysis should not drive therapy decisions for MPP patients.

**Prognosis**

Given the lack of validated prognostic parameters at the time of MPP diagnosis, no prognostic stratification of MPP patients has been established. Recent breakthroughs in genetics and imaging, as well as a median overall survival duration of more than 5 years in most studies, have made the prognostic characterization of these patients less straightforward (2, 8, 18).

Tumor progression is the most frequent cause of death from MPPs. This clearly indicates that controlling tumor growth should be the primary goal of MPP management (3, 8). However, manifestations such as hypertension and constipation, which are due to the abnormally high levels of catecholamines secreted by MPPs, cause up to 30% of MPP-specific deaths and should not be neglected. Finally, death from other cancers, although rare, should be considered, especially in the context of genetic syndromes (19, 20). The reported 5-year overall survival rates of MPP patients range from 40 to 77% (2, 8, 15, 18). One study found the presence of a SDHB mutation, after adjustment for tumor burden, to be the single most powerful prognostic factor, though this observation is yet to be confirmed (8). An extra-adrenal location of the primary tumor has also been proposed as a powerful prognostic factor for MPPs (2).

Retrospective studies evaluating the results of scintigraphy with MIBG in patients treated with chemotherapy and/or targeted therapies also illustrate the heterogeneity of MPP survival (19, 21, 22). These studies have reported progression-free survival durations ranging from 6 to 56 months, indicating a profound prognostic heterogeneity. In addition, one recent study has found that therapy-naïve patients have a 1-year progression-free survival rate of 50%, indicating a slow disease course in this subgroup of patients (18). Multivariate analyses adjusted for tumor burden,
genotype, and biochemical phenotype are urgently required to improve the prognostic stratification of MPP patients to rationalize timely therapeutic interventions.

**Treatment**

Once MPPs have been characterized, therapy options should be discussed in the setting of expert multidisciplinary meetings that include surgeons, interventional radiologists, endocrinologists, oncologists, and nuclear medicine physicians. The therapeutic arsenal for the treatment of MPP patients is small. Although therapy is expected to prolong survival and improve quality of life, gains in these areas are almost impossible to prove given the rarity of the cancer.

**Control of hormone- and tumor-related symptoms**

MPPs cause morbidity by invading and damaging organs and/or dysregulating the autonomic nervous system by secreting excessive adrenaline and/or noradrenaline. Three types of complications stemming from the damage and dysregulation highly affect clinical outcomes and therapeutic decisions in MPP patients: cardiovascular disease, gastrointestinal dysfunction, and skeletal-related events (SREs).

**Cardiovascular disease**—Patients with catecholamine-secreting tumors are frequently hypertensive and at risk of acute and chronic cardiovascular events. In addition, the chronic and excessive secretion of catecholamines may cause cardiomyopathy and congestive heart failure. Chemotherapy, molecular targeted therapies, and radiopharmaceutical agents destroy MPP cells and predispose patients to hypertensive crisis (23, 24). Therefore, these patients require adequate α- and β-adrenergic blockade. Phenoxybenzamine, a long-acting, nonselective (α1 and -2), noncompetitive α-adrenergic blocker, is the most commonly used agent. Selective α1-adrenergic blockers such as doxazosin and terazosin result in competitive receptor α1 antagonism (25). These readily available medications have shorter half-lives and are cheaper than phenoxybenzamine. β-adrenergic blockade should be instituted after the α-adrenergic blockade has been optimized (i.e., once the patient develops reflex tachycardia or orthostatic hypotension). Alternatives include calcium channel antagonists (e.g., nifedipine and amlodipine), angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors. α1-methyl-para-tyrosine inhibits catecholamine synthesis. This drug is frequently associated with overwhelming side effects such as anxiety, depression, fatigue, and diarrhea; in addition, it is expensive and difficult to obtain. Thus, this medication may be recommended to selected adult MPP patients in whom other medications are not able to normalize blood pressure and other symptoms of catecholamine excess (26). Although hypertensive, these patients are also hypovolemic and require fluid restoration and electrolyte balance. Somatostatin analog therapy has no proven effect on hormonal secretion.

**Gastrointestinal dysfunction**—The activation of α-receptors by catecholamines causes the contraction of splanchnic vascular smooth muscle and pyloric and ileocecal sphincters. On the other hand, the stimulation of β2 receptors by their primary ligand, adrenaline, causes intestinal smooth muscle relaxation. Thus, fecal material is retained in the gastrointestinal tract, and the progressive reabsorption of water results in dry, hard stools that can lead to severe constipation, obstruction, ulceration, perforation, and/or bacterial translocation. Some medications, such as opioids and vincristine, may exacerbate these symptoms. Gastrointestinal bleeding and perforation have also been described in patients treated with tyrosine kinase inhibitors (27).

Treatment for constipation may include oral fiber supplements, osmotic agents (e.g., lactulose and polyethylene glycol), lubricants and emollients (e.g., mineral oil and docusate), gastrointestinal stimulants (e.g., bisacodyl), α-blockers, α1-methyl-para-tyrosine, and/or enemas (28). If constipation persists despite these measures, ileostomy is recommended (29). Although metoclopramide is an effective prokinetic, its use is contraindicated in patients with catecholamine-secreting MPPs. In these patients, metoclopramide and serotonin agonists may precipitate a catecholamine crisis (30).

**Skeletal-related events**—Bone metastasis rates among MPP patients are as high as those observed in patients with more common tumors such as breast and prostate cancers (14). Approximately 70% of MPP patients develop bone metastases, including 20% who develop bone metastases exclusively (14, 19). Bone metastases are mainly lytic. Up to 80% of MPP patients with bone metastases develop SREs that include bone pain, pathological fractures, and/or cord compression; these patients rarely develop hypercalcemia (14). Hypercalcemia has been described as a late event associated with extensive bone metastases; however, it is unclear why this SRE is rare in patients with MPPs who predominantly have lytic metastases. Patients with bone metastases require a combination of therapeutic modalities including nonsteroidal anti-inflammatory agents, antiresorptive medications such as bisphosphonates or RANK-
ligand antagonists (e.g., denosumab), radiation therapy, laminectomy, ablation, surgical stabilization, and cementation (14). In all patients with bone metastases, the use of antiresorptive drugs may be considered as a preventive approach or as soon as SREs are observed. In a retrospective study carried out by Ayala-Ramirez et al., patients with MPPs treated with antiresorptives with or without systemic therapies exhibited significantly lower rates of SREs than patients with no intervention; in addition, the National Comprehensive Cancer Network recommends antiresorptive therapy for patients with other malignancies associated with lytic metastases (www.NCCN.org). Systemic therapies, which are associated with lower rates of SREs (14), are recommended for patients with large primary tumors and tumor progression (14). Surgery and radiation therapy are frequently needed. Thus, SREs must be treated by a multidisciplinary team. The current algorithm for the treatment of MPP patients with bone metastases is shown in Fig. 2.

Control of tumor growth

Tumor growth is another main concern in MPP patients. Only three published prospective clinical trials (two single-arm phase II and one phase I) have investigated strategies for curbing MPP growth (31, 32, 33). As a consequence, the optimal frontline therapy and sequence of therapeutic interventions for MPPs remain unclear (23). The benefit-to-risk ratio of each therapeutic option is the basis for several expert consensus statements (15, 23, 24). Bone marrow function should always be evaluated and spared. In patients with established malignancy, conventional imaging (CT/MRI) is considered the standard for tumor monitoring and evaluating therapeutic response (23, 34). Symptom improvement in association with a reduction of biochemical markers may indicate a therapeutic benefit. The following strategies should be considered for controlling tumor growth (Fig. 3).

Figure 2
The MD Anderson–Gustave Roussy algorithm for therapy against MPP bone metastases. *Consider antiresortive medications.

Figure 3
The MD Anderson–Gustave Roussy algorithm for first-line therapy against MPPs. *According to RECIST; **Protocols if available could be the first option; locoregional therapies and MIBG therapy constitute alternatives and their respective indication depends on the number, size, and anatomical location of metastases including the number of bone metastases as well the quality of MIBG uptake.
Locoregional guided therapy ▶ Locoregional guided therapy, including surgery, should be provided in the absence of radiographic tumor progression to avoid locoregional hazards such as spinal cord compression. Locoregional therapy could also be provided to decrease tumor burden in patients with multiple macroscopic osteolytic bone metastases and/or liver displacement of more than 30%. Interventional radiology paired with external conformational radiation beam therapy and/or surgery are key therapeutic options. In MPP patients with bone metastases, these interventions may control or prevent bone pain, decrease the rate of fractures, and prevent spinal cord compression as well as spare bone marrow function. Interventions such as surgery, radiotherapy, embolization, radiofrequency ablation, and cementoplasty should be considered for every bone metastasis (Fig. 3). Surgery may be considered to relieve the compression of neurological structures, resect the primary tumors, or, if other approaches fail to remove them, resect macroscopic tumors. As with systemic therapies, these patients require adequate α- and β-adrenergic blockade.

Targeted internal radiotherapy ▶ The most studied targeted radiotherapy in MPP patients is MIBG therapy. Because its structure is similar to that of noradrenaline, this radiopharmaceutical agent is taken up by the highly tissue-specific membrane noradrenaline transporter in MPP cells and then sequestered into vesicles, where it causes radiation-induced cell death. Approximately 50% of MPP patients are eligible for MIBG therapy (based on MIBG uptake on diagnostic imaging studies). Although many retrospective studies of targeted radiotherapy with MIBG have been published, only one phase II clinical trial of its use in treating MPP patients has been conducted (31, 36, 37, 38, 39). The results of the largest studies of MIBG therapy for MPP patients – those including at least 15 patients – are summarized in Table 2. Differences in MIBG activity, endpoints, and imaging modalities and insufficient clinical characterization of MPP patients make it impossible to compare these studies. The reported rates of tumor responses to MIBG therapy in MPP patients (defined using World Health Organization criteria, Response Evaluation Criteria in Solid Tumors, or non-standardized criteria) range from 22 to 48%. Of the MPP patients reported to have responded to MIBG therapy, 35–67% have been reported to exhibit a biochemical response. In the absence of specified tumor progression prior to therapy in all but one of these studies, the reported median progression-free survival durations, which range from 24 to 36 months, are not interpretable.

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of evaluable patients/tot al patients (patient accrual rate)</th>
<th>MIBG activity (mCi) (range)</th>
<th>Median no. of cycles (range)</th>
<th>Tumor response rate (%)</th>
<th>Methodology</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krempf et al. (37)</td>
<td>15/18 (3/year) Mean, 200 (80–250)</td>
<td>4 (2–11)</td>
<td>33</td>
<td>UK</td>
<td>Median PFS, 36</td>
<td></td>
</tr>
<tr>
<td>Safford et al. (36)</td>
<td>22/33 (2.2/year) Mean, 550 (70–1223)</td>
<td>1 (1–6)</td>
<td>38</td>
<td>UK</td>
<td>Median OS, duration, 42 months</td>
<td></td>
</tr>
<tr>
<td>Gedik et al. (38)</td>
<td>17/19 (0.8/year) Median, 200 (100–300)</td>
<td>3 (1–10)</td>
<td>47</td>
<td>UK</td>
<td>Median OS, duration, 42 months</td>
<td></td>
</tr>
<tr>
<td>Gonias et al. (31)</td>
<td>49/50 (3.3/year) Median, 818 (492–1160)</td>
<td>1 (1–3)</td>
<td>5–year OS rate, 47%</td>
<td>UK</td>
<td>Median OS, duration, 56 months</td>
<td></td>
</tr>
<tr>
<td>Wakabayashi et al. (39)</td>
<td>20/26 (4.5/year) Median first dose, 200 (UK)</td>
<td>2 (1–6)</td>
<td>27</td>
<td>UK</td>
<td>Median OS, duration, 42 months</td>
<td></td>
</tr>
</tbody>
</table>

OS, overall survival; WHO, World Health Organization; UK, unknown; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; EFS, event-free survival.
Main safety issues associated with MIBG therapy are asthenia, nausea, vomiting, hematologic and thyroid dysfunction, and, to a lesser extent, second cancer, hypertensive crisis, sepsis, and pulmonary toxicity (31, 36, 37, 38, 39). Patient deaths have also been reported (mainly due to bone marrow insufficiency/dysplasia). The ideal candidates for MIBG therapy as a first-line therapy are patients with significant tumor burden, slowly progressive disease, adequate MIBG uptake on diagnostic imaging, acceptable blood tests (absolute neutrophil count $\geq 1500/\text{mm}^3$, platelet count $\geq 100$ 000/\text{mm}^3, hemoglobin levels $\geq 9$ g/dl, bilirubin levels $\leq 1.5 \times$ the upper limit of normal (ULN), serum albumin levels $\geq 2.8$ g/dl, serum creatinine levels $\leq 1.5 \times$ ULN, and alanine aminotransferase and aspartate aminotransferase levels $\leq 3.0 \times$ ULN), and good performance status (23). The risk of hematologic toxicities in patients with multiple bone metastases should be carefully considered on a case-by-case basis.

Experience using $^{90}$Y-DOTATOC and $^{177}$Lu-DOTATOC, the two most often used radiolabeled agents that target somatostatin receptors, for targeted radiotherapy in MPP patients is limited. Two studies have shown that targeted radiotherapy with these agents elicits response rates of $<10\%$ (32, 40). This contrasts with the higher sensitivity of somatostatin receptor scintigraphy as a diagnostic imaging study compared with MIBG scintigraphy (41). The inappropriate expression of somatostatin receptor subtypes in MPP cells or processing errors may explain the lack of response to octreotide (42).

**Chemotherapy**

Noting that the embryological origin of MPPs is similar to that of neuroblastosomas, Averbuch et al. (43) proposed using the cyclophosphamide–vincristine–dacarbazine (CVD) regimen to treat MPP patients. The results of the largest studies investigating CVD therapy for MPP patients – those including at least 15 patients – are summarized in Table 3. In the first study carried out by Averbuch et al. (updated in 2008 (44)), the CVD regimen elicited partial or complete responses in 10 (55\%) of the 18 patients. Patel et al. (45) reported that a modified CVD regimen that included the optional use of vincristine combined with doxorubicin elicited a similar partial response rate (46\%) in 13 MPP patients. Recently, a group from the MD Anderson Cancer Center has reported a 25\% objective response rate using cyclophosphamide and dacarbazine and the optional use of vincristine or doxorubicin in 52 MPP patients (19). In a recent report from Japan, 8 (47\%) of the 17 evaluable MPP patients who received CVD therapy exhibited a complete or partial biochemical and/or tumor response (46). However, variations in endpoints and imaging modalities and insufficient patient characterization make comparing these studies impossible. No single prospective study has confirmed the results of any of these studies.

One alternative to the CVD regimen may be temozolomide, a 3-methyl analog of mitozolomide that was developed as an oral alternative to i.v. dacarbazine, the only drug of the CVD regimen well-recommended for the treatment of NET patients (47). Temozolomide is expected to have less toxicity than the CVD regimen. Recently, a team from the Gustave Roussy Institute has reported that the response rates of MPP patients on temozolomide therapy are similar to those of MPP patients on the CVD regimen (48).

Some MPP patients have died because of hormonal complications while receiving chemotherapy. Thus, the hormonal symptoms of MPP patients must be controlled before chemotherapy is initiated, and patients may need to receive their first cycles of chemotherapy in the hospital under close surveillance. Ideal candidates for the use of chemotherapy as a first-line therapy are those with rapidly progressive and/or symptomatic disease and adequate performance status and blood tests (23). In addition, for patients with multiple bone metastases, chemotherapy may have less toxicity compared with radiopharmaceutical agents.

**Molecular targeted therapies**

Few studies have investigated the use of molecular targeted therapies in MPP patients. In three different series, 11 patients treated with everolimus (49, 50) and two patients receiving imatinib (51) exhibited no response to targeted therapy. However, another study reported that one of three patients exhibited an objective response to thalidomide, an antiangiogenic agent, combined with oral dacarbazine (52). Case reports have described objective responses to sunitinib with manageable toxicity in a few MPP patients (53, 54).

More importantly, two large cancer referral centers’ combined experience in treating 17 patients (21) who had rapidly progressive MPPs with sunitinib revealed that 21 and 54\% of these patients exhibited responses based on the Response Evaluation Criteria in Solid Tumors or FDG-PET findings respectively. In addition, 43\% of the patients had their blood pressure under control, and some of these patients were able to discontinue antihypertensive medications. Three patients discontinued sunitinib therapy early owing to safety concerns about hypertension exacerbation, bone pain, and exacerbation of constitutional symptoms (i.e., fatigue). Intention-to-treat analysis revealed progression-free survival duration of
4.1 months. These observations indicate that the best possible control of hormone- and/or tumor-related symptoms must be achieved prior to the initiation of this systemic therapy. Preliminary experience from several other cancer centers indicates that antiangiogenic therapy shows promise; however, adverse events are common and sometimes severe leading to drug discontinuation or dose reduction. Thus, MPP patients should only be treated by clinicians who are familiar with the management of endocrine complications related to this disease and drug-related toxicities.

Table 3  Summary of retrospective series of chemotherapy enrolling at least 15 patients with malignant pheochromocytomas and paragangliomas.

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of evaluable patients/total no. of patients (patient accrual rate)</th>
<th>Treatment (dose)/duration</th>
<th>Median no of treatment cycles</th>
<th>Methodology</th>
<th>Tumor response</th>
<th>Response duration (months)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang et al. (44)</td>
<td>18/UK (1.6/year)</td>
<td>C (750 mg/m², D1) V (1.4 mg/m², D1) D (600 mg/m², D1–2)/21–28 days</td>
<td>18</td>
<td>Retrospective; WHO-like criteria</td>
<td>55% CR or PR</td>
<td>20</td>
<td>Median OS duration, 3.3 years</td>
</tr>
<tr>
<td>Ayala-Ramirez et al. (19)</td>
<td>52/54 (2.3/year)</td>
<td>C (600–750 mg/m²) D (750–1000 mg/m²) +/- Dx. (60–75 mg/m²) +/- V (1–2 mg/m²) 21–28 days</td>
<td>6.9</td>
<td>Retrospective; not standardized</td>
<td>25% PR</td>
<td>UK</td>
<td>5-year OS rate, 51%</td>
</tr>
<tr>
<td>Tanabe et al. (46)</td>
<td>17/23 (1/year)</td>
<td>C (750 mg/m², D1) V (1.4 mg/m², D1) D (600 mg/m², D1–2)/21–28 days</td>
<td>UK</td>
<td>Retrospective; not standardized</td>
<td>47% MR or PR</td>
<td>40</td>
<td>UK</td>
</tr>
<tr>
<td>Hadoux et al. (48)</td>
<td>15/15 (3.7/year)</td>
<td>TMZ 150–200 mg/m², D1–5/28 days</td>
<td>7</td>
<td>Retrospective; RECIST 1.1, PERCIST 1.0 used</td>
<td>33% PR</td>
<td>13</td>
<td>3-year OS rate, 55%</td>
</tr>
</tbody>
</table>

OS, overall survival; UK, unknown; D, day; C, cyclophosphamide; V, vincristine; D, dacarbazine; WHO, World Health Organization; CR, complete response; PR, partial response; Dx, doxorubicin; MR, molecular response; TMZ, temozolomide; RECIST, Response Evaluation Criteria in Solid Tumors; PERCIST, PET Evaluation Response Criteria in Solid Tumors.

Predictors of response

MIBG scintigraphy uptake and tumor location  Fifty percent of MPP patients have MIBG-avid tumors (22). These patients may benefit from treatment with 131I-MIBG. In previous studies, MIBG uptake has been defined without consensus as significant visual activity in the tumor. However, not all patients with MIBG-avid tumors exhibit a positive response to 131I-MIBG treatment. One study found that prior chemotherapy was a significant predictor of poor overall survival (31), probably because patients who had received chemotherapy had large, rapidly progressive tumors that were less sensitive to MIBG therapy. In addition, one review found that bone metastases were resistant to MIBG therapy (22), indicating that tumors located in soft tissues were the best candidates for responding to MIBG therapy.

Genotype  In the near future, genotype will probably be the main factor used to stratify MPP patients and determine therapeutic approaches. Preliminary evidence indicates that SDHB mutations have a potential role in the prediction of response to not only antiangiogenic therapy (21) but also chemotherapy and MIBG therapy (31). As has been

Predictors and surrogate markers of response

Preliminary clinical observations over the last 20 years have indicated that certain clinical, biochemical, genetic, and/or radiographic features help identify MPP patients who would benefit from specific systemic therapy (47). Randomized trials are necessary to validate predictors and surrogate markers of response in MPP patients.
discussed above, up to 50% of MPP patients carry germ line mutations in the SDHB gene (2, 8, 9, 10, 17). Tumors with these mutations are characterized by an increased angiogenesis (55). This characteristic indicates that antiangiogenic therapies could be used to treat patients with highly vascularized MPPs such as the SDHB-mutated tumors. One such therapy is sunitinib therapy, which targets vascular endothelial growth factor receptor 1/2 and platelet-derived growth factor receptor-β. In one recently published retrospective study (21), most of the patients who exhibited a positive response to sunitinib therapy were SDHB mutation carriers, and three of these patients exhibited a measurable drug response that lasted longer than 2 years. However, the sample for analysis was very small, and therefore it is not possible to conclude that SDHB mutations may predict a good therapeutic response to antiangiogenic therapies; in addition, whether patients with SDHB-mutated tumors respond better to sunitinib therapy than MPP patients without SDHB mutations needs to be evaluated in a larger, prospective, and comparative study.

Genotype has also been linked to chemotherapy efficacy against MPPs. Temozolomide has been found to have an antineoplastic action in O6-methylguanine-DNA methyltransferase (MGMT)-deficient tumors such as glioblastomas and gastroenteropancreatic NETs. MGMT plays a role in the cell detoxification process by relieving O6-methylguanine adducts. The recently published findings of researchers from the Gustave Roussy Institute and Hospital Georges Pompidou indicate that tumors associated with SDHB mutations are MGMT deficient and thus might respond better to CVD or temozolomide therapy than apparently sporadic tumors that are not associated with somatic mutations in the SDHB gene (48). Nevertheless, some carriers of SDHB mutations do not respond to CVD therapy (19).

Finally, Gonias et al. (31) reported that patients with SDHB mutations exhibited a high response rate to MIBG therapy. Indeed, some researchers anticipate discovering a common mechanism controlling the DNA methylation process of several genes in SDHB-mutated MPPs (56).

**Surrogates of response**

Additional measures that could be used to help personalize existing treatments and develop more effective therapies against MPPs potentially include evaluation of surrogates of response that include assessment of biochemical markers and FDG-PET changes during treatment (particularly for patients with no measurable disease) and evaluation of symptoms as predictors of antineoplastic effects.

**Future strategies for developing treatments against MPPs**

MPPs can be classified as either hereditary or sporadic tumors. This differentiation is important when considering the development of targeted therapies for the disease.

The majority of hereditary MPP cases are associated with germ line mutations of the SDHB gene. Although the molecular basis for this phenomenon is yet to be elucidated, SDHB-mutated tumors have an increased expression of other genes such as VEGF (VEGFA), MMP4, SIX1, and DSP as well as genes involved in the epithelial–mesenchymal transition, which are associated with tumor growth and local and distant invasiveness (57). These observations support preclinical and clinical studies investigating the use of drugs that target molecules involved in angiogenesis (e.g., vascular endothelial growth factor and platelet-derived growth factor), invasiveness (e.g., hepatocyte growth factor receptor), energy production (e.g., hexokinase), and oxygen metabolism (e.g., hypoxia-inducible factor and prolyl hydroxylases) as a potential treatment strategy in MPP patients.

With regard to sporadic MPPs, a recent study has revealed that 20% of sporadic pheochromocytomas and paragangliomas carry somatic mutations in the NF1 gene and that ~10% of these tumors are metastatic (58). These tumors are associated with the activation of downstream effectors of the Ras and kinase receptor pathways involved in cell differentiation, adhesion, and motility. Pathogenic somatic mutations of the RAS gene have been described in occasional cases of pheochromocytomas and paragangliomas. Although these mutations have not been found to be associated with malignancy, they emphasize the potential relevance of the Ras/mitogen-activated protein kinase and phosphoinositide 3-kinase pathways in MPP patients (59). Thus, the efficacy of inhibitors of tyrosine kinase receptors, Ras, mitogen-activated protein kinase kinase, and mammalian target of rapamycin against MPPs should be investigated.

Making therapeutic advances against MPPs, a very rare cancer that is associated with long survival duration, may be the most formidable challenge facing patients and clinicians. Indeed, the rarity of MPPs makes the feasibility of phase III clinical trials uncertain, and the long survival duration of MPP patients makes the demonstration of a proven survival benefit unlikely. Therefore, one may ask whether future recommendations for the treatment of MPP patients are condemned to be based only on the speculative analyses of retrospective studies. No simple answer to this question can be given. However, the
following recommendations may help to advance the understanding and treatment of MPPs:

1. MPP patients who undergo any kind of therapeutic intervention should be subject to a thorough, standardized characterization of their disease.

2. Therapeutic strategies used for MPP patients should be prospectively recorded, once patient permission is granted, in dedicated registries to minimize missing data.

3. Researchers should develop parallel single-arm phase II clinical trials with similar primary endpoints in which tumor progression prior to study entry is a major determinant of the treatment used.

4. The feasibility of randomized trials should be tested by implementing randomized phase II trials to investigate different treatment strategies for MPPs and assess the feasibility of future phase III trials.

5. All trials investigating MPPs should have a translational research element.

6. Clinical applications of next-generation sequencing technology in MPPs could help detect clinically actionable somatic/germline alterations of diagnostic, prognostic, or therapeutic significance.

These strategies are supported by multiple expert groups on different continents, international networking initiatives such as the European Network for the Study of Adrenal Tumors and the Pheochromocytoma and Paraganglioma Research Support Organization, and health authorities advocating for the simplification of drug development. A phase II study of Azedra (Progenics Pharmaceuticals, Tarrytown, NY, USA), a carrier-free MBG treatment, has been completed, and four ongoing phase II trials of sunitinib, dovitinib, axitinib, and pazopanib, including one randomized trial, are investigating the antitumor effects of antiangiogenic therapies in MPP patients. The primary endpoints of these trials are different; in the Azedra trial, the primary endpoint is blood pressure control, whereas the endpoints in the ongoing phase II trials are objective response rate (sunitinib, pazopanib, axitinib, and dovitinib) and progression-free survival (FIRSTMAPP Sunitinib Trial) (www.ClinicalTrials.Gov).

Researchers should view clinical trials not only as an opportunity to identify effective treatments for MPPs but also as an opportunity to better characterize the disease. Apart from assessing classical endpoints such as objective response rate, progression-free survival, and overall survival, such trials should include endpoints that could be used to inform individualized treatments and determine the optimal follow-up of patients receiving treatment.

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### Declaration of interest

E Baudin is the principal investigator in the FIRSTMAPP trial. The other authors declare no conflicts of interest.

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