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CLINICAL REVIEW: Current Treatment of Malignant Pheochromocytoma

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Context: Pheochromocytomas are rare tumors of predominantly adrenal origin that often produce and secrete catecholamines. Malignancy occurs in a variable percentage of cases depending on genetic background and tumor location. Definitive diagnosis relies on the detection of distant metastases. Treatments for malignant pheochromocytoma include surgical debulking, pharmacological control of hormone-mediated symptoms, targeted methods such as external irradiation, and systemic antineoplastic therapy. Different agents and protocols for this purpose are reviewed, and their therapeutic potential is discussed.

Evidence Acquisition: Literature on antineoplastic therapies for malignant pheochromocytoma was identified by searching the PubMed database with restriction to articles published in English during the past 30 yr.

Evidence Synthesis: Because of the rarity of the condition, no randomized clinical trials concerning the treatment of malignant pheochromocytoma have been performed. The strategy established best is [^{131}I]*meta*-iodobenzylguanidine (MIBG) therapy, which is well tolerated. Similar to cytotoxic chemotherapy with cyclophosphamide, vincristine, and dacarbazine, MIBG can induce remission for a limited period in a significant proportion of patients. Octreotide as a single agent seems to be largely ineffective.

Conclusions: MIBG radiotherapy and cyclophosphamide, vincristine, and dacarbazine chemotherapy are comparable with respect to response rate and toxicity. It is unclear whether combining both can improve the outcome. Future developments may include new multimodal concepts with focus on inhibition of angiogenetic factors and heat shock protein 90. Any present or new therapeutic approach must take into account the highly variable natural course of the disease. **(*J Clin Endocrinol Metab* 92: 1217–1225, 2007)**

PHEOCHROMOCYTOMAS (PCCs) are tumors of chromaffin cells that produce and often secrete catecholamines. They mostly occur within the adrenal medulla but may also present as paragangliomas (PGLs) of the extraadrenal sympathetic nervous system, occurring in the chest, abdomen, or pelvis (1). Despite a comparatively high prevalence in some autopsy studies (2–4), PCCs are discovered during life in only one to six per million people/yr among the general population (5–9). Most tumors are sporadic, but about 25% of cases are associated with germline mutations in one of five major susceptibility genes (10–13). This etiological diversity is reflected by considerable variations in the biological behavior of chromaffin cell tumors (14).

The frequency of a malignant course depends strongly on the genetic background. There is a particularly high risk of malignancy for tumors caused by mutations in the gene for succinate dehydrogenase subunit B (SDHB). In a recently reported series of patients, SDHB-related PCCs were malignant in 15 of 21 cases (11). Mutations in the gene for subunit D (SDHD), in contrast, are associated with a much lower rate of malignant PCCs (11, 15–17). Also, virtually all PCCs in multiple endocrine neoplasia (MEN) type 2, more than 90% of those in von Hippel-Lindau disease (VHL), and almost 90% of those in neurofibromatosis type 1 (NF-1) appear to be benign (11, 18–21). Although the phenotype is more aggressive in MEN type 2B than in MEN type 2A with regard to medullary thyroid carcinoma, this relation has not been proven for PCC.

Chromaffin cell tumors in MEN type 2, von Hippel-Lindau disease and neurofibromatosis type 1 have predominantly intraadrenal locations, whereas those in patients with SDHD and SDHB mutations have predominantly extraadrenal locations. However, PGLs metastasize more often than adrenal PCCs even in genetically unselected collectives (22–26). Thus, the higher prevalence of malignancy in PGL cannot be explained by an association of genetic background and tumor site alone. Extraadrenal location should therefore be recognized as an independent determinant of the risk of malignancy, although published data on this aspect are not unequivocal (27).

Several biochemical (28–30), morphological (31–34), and molecular (35–39) markers for distinguishing benign and malignant PCCs have been investigated, but none appear to reliably indicate malignant behavior. The only criterion for malignancy generally agreed upon is the presence of chromaffin tissue, unconnected with the primary tumor, at sites where chromaffin tissue is normally absent, *i.e.* the presence

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Abbreviations: CVD, Cyclophosphamide, vincristine, and dacarbazine; ^{90}Y-DOTATOC, [^{90}Y-DOTA]-D-Phe^{1}-Tyr^{3}-octreotide; MEN, multiple endocrine neoplasia; MIBG, *meta*-iodobenzylguanidine; PCC, pheochromocytoma; PGL, paraganglioma; SDHB, succinate dehydrogenase subunit B; SRI, somatostatin receptor imaging; sst, somatostatin receptor.

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of distant metastases (40). As a consequence, the diagnosis of malignant PCC currently excludes the possibility of surgical cure. Surgical debulking is nevertheless widely regarded as a mainstay of palliative therapy despite lack of data (41). The rationale behind this approach is to reduce exposure of target organs to high levels of catecholamines and, if [^{131}I]*meta*-iodobenzylguanidine (MIBG) radiotherapy (see below) is feasible, to increase the relative uptake of MIBG into the remaining lesions. It is unclear, however, whether tumor debulking is useful if catecholamine release is low and MIBG uptake is unappreciable by imaging studies.

Prognosis in cases with confirmed malignancy is difficult to predict, both for sporadic and familial PCCs. Although there is no difference in overall survival between adrenal and extraadrenal malignant PCC, the outcome worsens with increasing tumor size in both groups (23, 27). Average 5-yr survival in the presence of metastases, which typically affect the bones, liver, lungs, and lymph nodes (42, 43), is approximately 50% (25, 40). Pharmacological control of the physiological and pathological effects of excess circulating catecholamines represents a continuing requirement in the treatment of metastatic or incompletely resectable invasive PCCs. α-Adrenergic receptor blockers and calcium channel antagonists often reduce hormone-mediated symptoms sufficiently, but occasionally additional treatment with α-methyl paratyrosine to inhibit catecholamine synthesis is necessary (44). External irradiation and other targeted methods (such as radiofrequency ablation, cryoablation, and arterial embolization) can help to alleviate local complications (40). However, these approaches are purely for symptomatic relief. Considerable attention has therefore focused on the development of systemic antineoplastic therapies. In the following sections, we summarize the effects of different agents that have been administered for this purpose, and the question will be addressed whether or not treatment with these substances should be initiated in individual cases.

Sources

The PubMed database was searched on March 1, 2006, for articles on the antineoplastic therapy of malignant pheochromocytoma published between January 1, 1976, and January 31, 2006. Only papers written in English were considered. The medical subject heading pheochromocytoma was used alone and in combination with the medical subject headings antineoplastic protocols, MIBG, or octreotide to identify relevant references. Independent of these categories, additional articles with particular relevance to the topic were also included.

Preliminary Remark

Evaluation criteria for the response to antineoplastic therapy are not uniform in the reviewed studies. We use here the following common definitions (45). 1) For tumor response, a complete response reflects the disappearance of all radiological evidence of the tumor; a partial response is defined by at least a 50% decrease of the size of all tumor lesions (measured by computed tomography or magnetic resonance imaging), without reaching a complete response, and includes the absence of new lesions on computed tomography, magnetic resonance imaging, or scintigraphic scans; and progression is defined by at least a 25% increase of the radiological size of any tumor lesion or by the visualization of at least one new lesion. 2) For biochemical response, a complete response results if all major biochemical markers used for evaluation (such as plasma or urinary catecholamines or metanephrines) have normalized; a partial response is defined by at least a 50% decrease, but not normalization, of these markers; and progression is defined by at least a 25% increase of any major biochemical marker. For measurements of catecholamines, this definition could be impacted by variable amounts of catecholamines secreted by tumors. In contrast, levels of metanephrines, which are produced independently of variations in catecholamine release and show strong positive relationships with tumor volume, should provide more accurate measures of biochemical response in terms of tumor catecholamine synthesis (*i.e.* catecholamine production) (46).

All other courses are classified as stable disease.

Chemotherapy

Cytotoxic chemotherapy was the first antineoplastic principle employed in malignant chromaffin cell tumors. Early attempts with streptozocin in two patients with inoperable PCC were unsuccessful both biochemically and morphologically (47), whereas a partial biochemical remission and a reduction of the adrenal mass by 25% and of a hepatic metastasis by 50% was observed later in a single case (48). Streptozocin was also administered to one patient with a metastatic PGL of the organ of Zuckerkandl, resulting in a partial biochemical response, but ultimately fatal tumor progression (49). Combined chemotherapy with streptozocin, cyclophosphamide, and 5-fluorouracil resulted in a slight biochemical improvement at formally stable disease in one of two patients with metastatic PCC (50).

A new and more effective protocol was introduced in 1985 by Keiser *et al.* (51), who employed a combination of cyclophosphamide, 750 mg/m^2 body surface area on d 1; vincristine, 1.4 mg/m^2 on d 1; and dacarbazine, 600 mg/m^2 on d 1 and 2, with this protocol repeated every 21 d [cyclophosphamide, vincristine, and dacarbazine (CVD) scheme]. In 1988, these investigators published a nonrandomized study of 14 patients with metastatic PCC receiving this therapy (52). Two patients had a complete and six a partial tumor response with a median duration of 21 months. A biochemical response was documented in 11 patients (median duration, 22 months). Remarkably, only one patient had continuous tumor progression from the initiation of chemotherapy (which was stopped after four cycles). In this trial, cyclophosphamide and dacarbazine dosages were increased by 10% each cycle until bone marrow suppression occurred, whereas treatment delays for 1 wk or dosage reductions were made in case of hematological or neurological side effects. Toxicity was mild to moderate and included leuko- and thrombocytopenia, paresthesias, nausea, and vomiting. No serious adverse events were noted. A number of case reports have subsequently confirmed the short-term benefit and the tolerable side effects of the CVD scheme; however, relapse occurred within 2 yr in most of these patients (26, 44, 53–56).

Different chemotherapy protocols were tested in small numbers of patients. One patient displayed a reduced need of antihypertensives after cisplatin and 5-fluorouracil combination therapy (57). A male patient with a cardiac PGL histologically considered malignant because of micrometastases in adjacent lymph nodes was treated with vepeside, carboplatin, vincristine, cyclophosphamide, and adriamycine as adjuvant therapy after resection and has remained disease-free for 5 yr (58). A regimen adding anthracyclines to a modified CVD therapy was effective in a case of adrenal PCC with distant lymph node metastases (59), with continuous remission 3 yr after cessation of chemotherapy. Bone marrow suppression was the most serious side effect. Very recently, a radiological response was reported in one of three cases of metastatic PCC among 29 patients with neuroendocrine tumors treated with an oral regimen of temozolomide (median dose, 150 mg/d) and thalidomide (median dose, 100 mg/d) (60). Notable toxic effects in the whole study population included lymphocytopenia (69%), thrombocytopenia (14%), and neuropathy (38%).

In summary, the CVD scheme seems effective at modest toxicity in a significant proportion of patients (Table 1), although remissions are rather short (≤2 yr) and are often followed by complete therapeutic failure after relapse. Data on other protocols remain limited.

MIBG Radiotherapy

MIBG (Fig. 1), a guanethidine analog, is selectively concentrated in chromaffin storage granules due to uptake by the same mechanisms responsible for uptake and storage of catecholamines (61). The agent, however, has no affinity for adrenergic receptors. Therapeutic application of ^{131}I-labeled MIBG, which acts mainly through emission of β-particles, was introduced in 1983 (62–64) and since then employed in numerous patients with malignant PCC (43, 54, 65–87).

Loh *et al.* (88) reviewed 116 patients treated with [^{131}I]MIBG before 1997, including 89 patients of whom follow-up data were available. Among the latter, death was reported in 33% of those with an initial response to MIBG after a median of 22 months after treatment and in 45% of the nonresponders after a median of 13 months. Individual doses typically ranged from 3.7–7.4 GBq and were repeatedly administered at intervals of several months. In terms of imaging (computed tomography, MIBG, or bone scintigraphy), complete or partial remission was induced in 4% and, respectively, 26% of all the 116 patients, whereas in 57%, no relevant changes were noted. Progression was evident in 13%. Biochemical data were available from 96 individuals who had complete normalization of urinary catecholamines or their metabolites in 13% of cases, partial normalization in 32%, and unchanged or increasing values in 55% of cases.

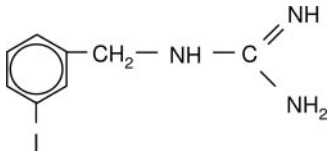

FIG. 1. Structural formula of MIBG.

From extended analyses based on this work (89, 90), it was concluded that [^{131}I]MIBG therapy induces (mostly partial) tumor responses in 24–45% of the patients, among whom disease progression after approximately 2 yr is common. Toxicity is generally modest and mainly affects the bone marrow, most often with thrombocytopenia occurring within a few weeks of treatment. Myeloid leukemia as a secondary malignancy has been observed in two of 119 children treated with MIBG for neuroblastoma (91); however, no conclusive data are available on the frequency of leukemia after MIBG treatment for malignant PCC. Nausea is typical, and impaired liver and thyroid function have also been reported (90).

Preparation with sodium perchlorate or potassium iodide is necessary 2 d before and 1 wk after MIBG therapy to protect the thyroid gland (see Table 3). Also, drugs that interfere with MIBG uptake, such as labetalol, reserpine, digoxin, angiotensin converting enzyme inhibitors, various antidepressants and antipsychotics, and some sympathomimetics, should be withdrawn 3–10 d before MIBG treatment (92–95).

High-dose therapy

Usually, multiple medium doses of [^{131}I]MIBG of about 200 mCi (7.4 GBq) are administered. Increased long-term survival may be achieved with higher individual doses, as suggested by Rose *et al.* in 2003 (96). Twelve patients were

TABLE 1. CVD chemotherapy for malignant PCC (selected reports)

Publication year (ref.)	No. of patients	Biochemical response (%)		Tumor response (%)		Stable disease (%)	Progression (%)
		Complete	Partial	Complete	Partial		
1988 (52)	14	21	57	14	43	36	7
1996 (55)	2	0	50	50	0	50	0
1998 (44)	3	NE	NE	0	0	33	67
1999 (86)[a]	4[b]	0	0	0	50	0	50
2001 (87)[c]	3	33	0	0	33	67	0
2003 (26)	4	ND	ND	25	25	25[d]	25
% of evaluable cases		20	45	14	32	36	18

The best response is listed irrespective of later relapse. Stable disease and progression refer to tumor presence only. ND, No data available; NE, not evaluable due to concomitant application of α-methyl tyrosine.

[a] Chemotherapy was initiated 3–5 months after MIBG therapy in all patients.

[b] Tumor response was evaluable in two patients, and biochemical response was evaluable in one patient.

[c] Chemotherapy was initiated 5 months after MIBG therapy in one patient.

[d] Complete remission of lung metastases in this patient.

treated with a median single dose of 29.6 GBq and a median cumulative dose of 37.6 GBq. Three of those patients had a complete remission, including two with soft tissue and bone metastases, and seven patients had a partial response. Median follow-up for the responders was approximately 3.5 yr. The two nonresponders and two of the patients with a partial remission died from progressive disease after approximately 1 yr. The main toxic effects were severe thrombocytopenia and neutropenia, with one patient requiring infusion of stem cells harvested routinely before high-dose treatment. Because increased hematotoxicity is an important disadvantage of high-dose compared with low- or medium-dose MIBG therapy (which might even outweigh an improved response rate), prospective studies are required to evaluate the overall outcome of treatment with different MIBG doses. Perhaps multiple medium-dose treatments (with cumulative doses up to 66.6 GBq) could provide an effective but less toxic alternative to high individual doses (97).

Combination with chemotherapy

Sisson *et al.* (86) suggested additive effects of combined [^{131}I]MIBG treatment and subsequent 1-yr CVD chemotherapy in a study including six patients. Only one patient, who had a partial tumor response, completed the whole study protocol. A second patient received 9 months of chemotherapy after MIBG therapy and had a partial biochemical response but could not be evaluated radiologically for technical reasons. Three patients had progressive disease, one of whom did not finish MIBG treatment; another patient refused to return for chemotherapy. Altogether, a benefit of additional chemotherapy could not be demonstrated. Based on observations in one of six patients reported, Hartley *et al.* (87) proposed MIBG uptake might increase after a partial radiological response to chemotherapy. Although earlier experimental findings in neuroblastoma cell lines treated with doxorubicin and cisplatin (98) support this hypothesis to some extent, it has not been tested further in a clinical setting.

In summary, [^{131}I]MIBG therapy remains regarded as a valuable option with low toxicity in malignant PCC. Application of a high radiation dose, as described above, appears to increase both effectivity and toxicity with unknown impact on the overall outcome. Compared with CVD chemotherapy, published experience with MIBG is more extensive (Table 2) and implies at least equally long remissions among the responders, who represent 25–30% of the qualified patients. Overall, it is uncertain which of the two treatments possesses a higher initial response rate. However, patients who will definitely not benefit from [^{131}I]MIBG because of insufficient uptake of the radiopharmaceutical can be identified in advance by diagnostic scintigraphy. Such patients are eligible for chemotherapy, as discussed earlier.

Somatostatin Analogs

In patients with endocrine tumors expressing somatostatin receptors, targeted treatment with analogs of the natural ligand can lead to marked biochemical and, in part, radiological improvements (99, 100). Octreotide and lanreotide are somatostatin-like oligopeptides that are widely employed in the therapy of somatotropin-secreting pituitary adenomas and neuroendocrine tumors of the gastroenteropancreatic system. These analogs in radiolabeled forms (usually [^{111}In] pentetreotide) are also useful for somatostatin receptor imaging (SRI) (101). Many adrenal and extraadrenal PCCs are positive in SRI, and interestingly, this is often also true for MIBG-negative metastatic lesions (101–103), suggesting a possible therapeutic role for somatostatin analogs. However, data concerning this approach are scarce.

An immediate effect of octreotide on plasma norepinephrine levels could be shown in a study including six patients with chromaffin cell tumors (104). Octreotide was given iv for 2 h at a dose of 50 μg and led to a significant decrease of plasma norepinephrine by 50% during the infusion. Blood pressure remained unaltered in five patients and was lowered transiently in one. No sustained effects were noted. In a placebo-controlled crossover study, 10 patients with resectable PCC received three sc injections of either 100 μg octreotide or vehicle (105). There was no specific effect of octreotide on plasma or urinary catecholamine or neuropeptide Y levels, or on blood pressure, during the 24-h test interval.

TABLE 2. MIBG radiotherapy for malignant PCC (selected reports)

Publication year (ref.)	No. of patients	Biochemical response (%)		Tumor response (%)		Stable disease (%)	Progression (%)
		Complete	Partial	Complete	Partial		
1997 (88)[a]	116[b]	13	32	4	26	57	13
1999 (89)[a]	137[c]	43[d]	43[d]	6	18	55	21
1999 (86)	6	17	17	0	33	33	33
2001 (87)[e]	6[f]	0	20	0	0	67	33
2003 (96)[g]	12[h]	33	50	18	18	45	18
% of evaluable cases[i]		13	32	4	25	56	15

The best response is listed irrespective of later relapse. Stable disease and progression refer to tumor presence only.
[a] Review of publications since 1983, additional report on three own patients in (88).
[b] Biochemical response evaluable in 96 patients.
[c] Includes patients from Ref. 88; biochemical response evaluable in 120 patients.
[d] No differentiation was made concerning complete and partial biochemical responses.
[e] First-line treatment in three patients, the other three receiving chemotherapy first (two CVD, one vincristine/ifosfamide/cisplatin).
[f] Biochemical response evaluable in five patients.
[g] High dose therapy (one to three treatments, cumulative dose 14.3–63.5 GBq).
[h] Includes two patients from Ref. 88; biochemical response evaluable in six, tumor response evaluable in 11 patients.
[i] Patients reported more than once were accounted for.

TABLE 3. Overview of different antineoplastic treatment options for malignant PCC

Treatment modality	Indications		Toxicity[a]	
	For first-line use	For second-line use	Effect	Precautions
CVD chemotherapy	Rapidly progressive disease	Progressive disease	Massive catecholamine release (catecholamine storm) after ≤48 h	Hospitalization for first cycle
			Bone marrow suppression[b] after ≥10 d	Ambulatory WBCs
MIBG radiotherapy (standard dose)	Slowly progressive disease with predominantly MIBG-accumulating lesions	Progressive disease with predominantly MIBG-accumulating lesions	Hypothyroidism[c]	Blockade of iodine uptake (with $NaClO_4$ and/or KI)[c]
			Bone marrow suppression[b] after few weeks	Ambulatory WBCs
MIBG radiotherapy (high dose)	As above, should be considered if MIBG-accumulating bone or soft tissue lesions are present	As above, should be considered if MIBG-accumulating bone or soft tissue lesions are present	Bone marrow suppression (severe thrombocytopenia and neutropenia) after 18–41 d	Routine stem cell harvest, ambulatory WBCs
Somatostatin analog therapy (including radiotherapy)	None	Progressive disease with SRI-positive lesions and failure of other modalities	Renal failure (DOTATOC radiotherapy)	Fluid substitution, omit nephrotoxic medication
			Gallstones (long-term treatment)	

Sodium perchlorate ($NaClO_4$, *e.g.* 300 mg thrice daily in adults), potassium iodide (KI, *e.g.* 130 mg once daily in adults). WBC, Whole blood count.

[a] Some typical effects that need special consideration are listed here. For other aspects of toxicity see main text.

[b] Usually thrombocytopenia.

[c] Applies to both standard- and high-dose therapy.

A single case of a male patient with a PCC whose hypertensive episodes could only be controlled with octreotide (300 μg/d sc) was reported (106). A reduction of serum and urinary catecholamines was documented during octreotide treatment. It cannot be ruled out, however, that these clinical and biochemical improvements were due to spontaneous fluctuations of catecholamine release or to a placebo effect; little evidence supports the authors' conclusion that octreotide is useful in some patients with uncontrolled hypertension caused by a PCC.

Indeed, a more recent and well-designed trial strongly suggests that octreotide is ineffective in these tumors. Lamarre-Cliche *et al.* (107) treated 10 patients with malignant or recurrent PCC with slow-release im octreotide, 20 mg once monthly, and recorded clinical and biochemical markers of tumor activity before the first and 4 wk after the third injection. No changes in major parameters, particularly blood pressure, plasma catecholamine and chromogranin A concentrations, and metanephrine excretion, were noted. Symptoms remained equally unaffected. Because all patients had received SRI before octreotide administration, the authors could also show that these clinical and biochemical findings did not depend on the presence or absence of [^{111}In]pentetreotide uptake.

The ineffectiveness of octreotide may be due to the expression of different somatostatin receptor (sst) subtypes in PCCs, of which only one, sst2a, binds standard somatostatin analogs with high affinity. In a large series of 52 PCCs from 35 patients, Mundschenk *et al.* (108) found positive immunohistochemical staining for sst2a in only 25% of the tumors, whereas sst3 was expressed in 90%. Other subtypes were even less frequent than sst2a. Among those patients who had received SRI before surgery, scintigraphy was true-positive if either sst2a or membrane-associated sst3 was present. In another study, not only was sst3 expression found in all of seven PCCs, but staining was also observed for more than 60% of the cells in each tumor (109). Whether a subgroup of SRI-positive patients may benefit from new somatostatin analogs with an improved affinity for sst3, such as SOM230 (110), remains to be elucidated.

Neuroendocrine tumors have also been targeted therapeutically with radiolabeled octreotide derivatives, such as [^{111}In]pentetreotide and [^{90}Y-DOTA]-D-Phe^1-Tyr^3-octreotide (^{90}Y-DOTATOC) (111). Because few patients harboring a malignant PCC have been treated this way, data are not sufficient to evaluate this approach. Impaired renal function and bone marrow suppression are common side effects of [^{90}Y]DOTATOC (112). Thus, compared with MIBG therapy, the lack of organ specificity and a considerable toxicity are disadvantageous.

Conclusion and Perspectives

There is no generally effective systemic treatment with antineoplastic potential for malignant PCC. A considerable proportion of the patients respond to MIBG radiotherapy or to cytotoxic chemotherapy. However, because there are no published randomized controlled studies, it remains unclear whether these responses have an overall impact on survival or quality of life. Initial delay of disease progression might

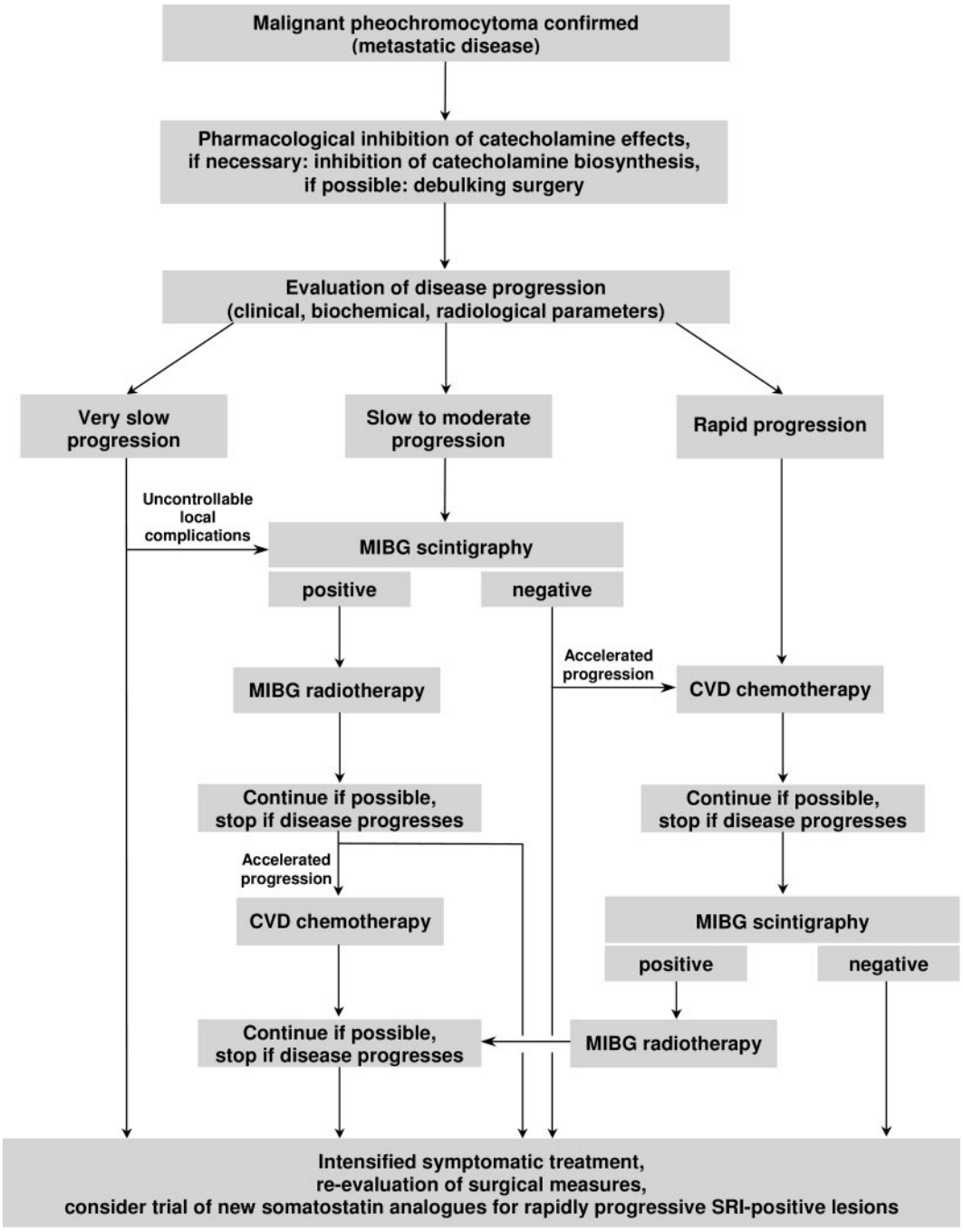

FIG. 2. Proposed algorithm for the treatment of metastatic pheochromocytoma.

be compensated by accelerated tumor spread after secondary failure of antineoplastic therapy, and side effects of the latter could outweigh symptomatic improvements related to reduced tumor burden (Table 3).

Although most patients with a malignant PCC experience rapid expansion of primary and metastatic tumor tissue, progression may be extremely slow in others, even after generalization of the neoplasm. Survival for 26 yr after diagnosis of bone metastases has been reported without antineoplastic treatment (113). Therefore, any present or new therapeutic approach must take into account the highly variable natural course of the disease. It must be stressed that, due to the lack of evidence, a potentially harmful antineoplastic therapy is a particularly questionable option for those who have minimal symptoms and in whom long-term survival is likely (although there is no single parameter by which the extent of future tumor cell growth can be predicted, the combination of clinical, biochemical, histological, and radiological findings usually allows a preliminary estimate). Consequently, this subgroup of patients is infrequently treated by radio- or chemotherapy.

For the remaining majority of patients, suffering from ad-

vanced local and metastatic disease, informal algorithms concerning antineoplastic treatment have emerged with growing clinical experience (41). In rapidly progressive metastatic PCC, chemotherapy should be used as first-line therapy. Only the CVD scheme has been applied more than sporadically and is therefore the protocol of choice. If progression is slower, [^{131}I]MIBG therapy has become the preferred approach for patients with a positive MIBG scan, because its effectivity and toxicity are more precisely known than for any other strategy, and both are acceptable. On the other hand, negative diagnostic scintigraphy predicts unresponsiveness to this treatment. Thus, MIBG administration can be omitted in these cases, and cytotoxic chemotherapy should instead be considered as the first-line therapy in cases of accelerated progression (Fig. 2). Currently, chemotherapy is also offered after primary or secondary failure of [^{131}]MIBG therapy, but little is known about its disease-limiting potential under these circumstances. MIBG radiotherapy should also be offered to patients with severe local complications of irresectable MIBG-accumulating tumors (such as large functional PGLs of the heart), even if progression is very slow and metastatic tumor burden low.

Future strategies may include some of the developments mentioned earlier, such as new chemotherapies, combinations of chemotherapy and [^{131}]MIBG therapy, increased doses of [^{131}]MIBG, radiotherapy with somatostatin analogs, or introduction of somatostatin analogs with enhanced binding to different receptor subtypes. Valuable information may also be drawn from treatment trials of neuroblastoma with MIBG or somatostatin analogs (114). In addition, new targets will be identified. Whether heat shock protein 90 (hsp90) is a promising candidate in this context remains to be elucidated. This molecular chaperone is overexpressed in malignant PCCs (38) and appears to serve as an important determinant of human telomerase reverse transcriptase (hTERT) expression, which is also enhanced in these tumors (37, 38). Inhibition of angiogenic pathways may also be an important element of multimodal concepts for therapy of malignant PCCs (35, 36, 115–117).

With the successful completion of the human genome project and the growing advance in genomic and proteomic research, our understanding of the basic mechanisms underlying the development and progression of both sporadic and familial malignant PCC will improve at increasing speed, probably leading to pathway-specific therapeutic strategies tailored to the individual biological background in each patient (40). Clearly, multicenter (and multinational) randomized trials are necessary to answer the questions connected with this expanding knowledge and to develop evidence-based standards to treat malignant pheochromocytoma more efficiently than previously possible.

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