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CLINICAL TRIAL REPORT

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Successful treatment with paclitaxel of a patient with metastatic extra-adrenal pheochromocytoma (paraganglioma)

A case report and review of the literature

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Abstract This case report describes the history of a patient with an aggressive course of a metastatic extra-adrenal pheochromocytoma (paraganglioma) who received different combination chemotherapy regimens with no or short-lasting clinical benefit. However, during treatment with single-agent paclitaxel, there was a significant clinical improvement, a partial biochemical response and a minor roentgenologic response, which was sustained for 1 year. In this report we present this case and also review the literature on the chemotherapy used for this rare disease over the past 15 years. To enable the activity of paclitaxel against this neoplasm to be determined, more patients need to be treated.

Key words Extra-adrenal pheochromocytoma · Chemotherapy · Paclitaxel · Paraganglioma

Introduction

Paragangliomas are uncommon tumors which can arise from the neuroectodermally derived paraganglionic cells associated with the autonomic nervous system. The paraganglion system includes the adrenal medulla and the extra-adrenal paraganglion system. The components of the latter are described according to their anatomic location as (1) brachiomeric, (2) intravagal, (3) aortic-sympathetic and (4) visceral-autonomic [7]. Of the extra-adrenal tumors, 25–60% are functional [17] with signs and symptoms of overproduction of catecholamines and are also called extra-adrenal pheochromocytomas. These tumors can be malignant (10%) and metastasize to bone, liver, lymph nodes, lung and peritoneum. The treatment of choice for this malignancy is surgical resection and, for those with signs and symptoms of excess circulating catecholamines, medical therapy with α- and β-blocking agents must be prescribed [12, 21]. When surgery is not feasible, combination chemotherapy can be applied, but with limited effectiveness. In this report we discuss the history of a male patient with a metastatic extra-adrenal pheochromocytoma (paraganglioma) who received different chemotherapy regimens. We also review the literature on the chemotherapy used for this disease during the last 15 years.

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Case report

In August 1996 a 24-year-old male patient with no previous medical history was admitted to a regional hospital because of fever, fatigue, headache, sweating, loss of weight and persistent right flank pain. Physical examination revealed a sick young male with a temperature of 38.5 °C, a blood pressure of 230/155 mmHg, a regular pulse of 100/min and a right-sided palpable abdominal mass. Laboratory analysis showed only a high sedimentation rate (75 mm/h). Computed tomography of the abdomen and thorax revealed a suprarenal mass on the right side of 15 cm with heterogeneous density and small areas of calcifications, enlarged retroperitoneal lymph nodes and pulmonary metastases. Urinary vanillylmandelic acid (VMA) excretion was increased to 1200 μmol/24 h (normal <40 μmol/24 h). A lumbotomy with histologic biopsy confirmed the diagnosis of an extra-adrenal pheochromocytoma. He was started with α- and β-blockade (phenoxybenzamine and atenolol, respectively) to control his hypertension and tachycardia, which resulted in symptomatic relief. For staging a bone scintigraphy was performed, which showed multiple bone metastases. Scintigraphy with ^{131}I metaiodobenzylguanidine (^{131}I-MIBG) also showed increased uptake of radioactivity in the liver, suggestive of liver metastases.

The diagnosis of the patient was extra-adrenal pheochromocytoma with metastases to bones, lungs, liver and retroperitoneal lymph nodes and a primary tumor at the right suprarenal site. Additional tests performed to exclude medullary thyroid carcinoma (pentagastrin stimulation test), hyperparathyroidism (serum parathormone) were all negative. There was no family history of MEN-2 syndrome (multiple endocrine neoplasia-type 2). He received a

Table 1 Review of combination chemotherapy in patients with metastatic (extra-adrenal) pheochromocytoma (paraganglioma). Biochemical response was defined as >50% reduction of urine measurements (*CDDP* cisplatin, *CTX* cyclophosphamide, *DOX* doxorubicin, *STZ* streptozotocin, *VCR* vincristine; *CR* complete response, *MR* minor response, *PD* progressive disease, *PR* partial response, *SD* stable disease; *NS* not stated, + metastases present, sites not described)

Reference	Drugs	Dosage (mg/m^2)	Schedule (every *n* weeks)	No. of patients	Sites of disease	Response		Survival (months)
						Biochemical (*n*/%)	Lesions (*n*/%)	
2	5-FU, CTX, STZ	500 (days 1, 8)	3	2	Bones	PR (2)	SD	16
					Lymph nodes		SD	36
1	CTX	750 (day 1)	3	14	Bones, lymph nodes, lungs, liver	CR + PR (11/79%)	CR + PR (8/57%)	NS
	VCR	1.4 (day 1)						
	Dacarbazine	600 (days 1, 2)						
15	CTX, VCR, DOX, Dacarbazine	Same as ref. 17	3	1	Bones, chest wall	NS	PR	NS
20	CTX, VCR, Dacarbazine	Same as ref. 1	3	1	Bones	PR	MR	45
18	VP 16, CDDP	Unknown		1	+	SD	SD	NS
	CTX, VCR, Dacarbazine	Same as ref. 1	3	1	+	PR	PR	NS
14	CTX	750 (day 1)	4	1	Bones, spinal cord	NS	PR	24
	VCR	1.4 (day 1)						
	Dacarbazine	600 (days 1, 2)						
	↓							
	Carboplatin	300	4			NS	MR	
	↓							
	CDDP	25 (days 1–3)				NS	PD	
	Etoposide	100 (days 1–3)						
17	*A:* CTX	600–750 (day 3 or 5)	3	7	Bones, lymph nodes	NS	PR (5/71%)	NS
	DOX	60–90 (days 1–2 or 1–4)			Brain		SD (2/39%)	
	Dacarbazine	900–1000 (days 1–2 or 1–4)						
	B: CTX	600–750 (day 3 or 5)	3	4	Bones, liver	NS	PR (1)	NS
	DOX	60–90 (days 1–2 or 1–4)			Lymph nodes, lungs		SD (3)	
	Dacarbazine	900–1000 (days 1–2 or 1–4)						
	VCR	1.4 (day 1)						
	C: DOX	60–90 (days 1–2 or 1–4)	3	2	Lymph nodes, bones	NS	SD (1)	NS
	Dacarbazine	900–1000 (days 1–2 or 1–4)			Lungs		PD (1)	
16	CTX, VCR, Dacarbazine	Same as ref. 1	3	2	Bones	PR (2)	CR (1)	33
					Lungs		SD (1)	NS
13	CTX, VCR, Dacarbazine	Same as ref. 1	3	1	Liver	MR	MR	17

therapeutic dose of 45 MBq ^{131}I-MIBG because of the high uptake of the diagnostic tracer dose with no signs of improvement. Subsequently, he received combination chemotherapy consisting of cyclophosphamide 750 mg/m^2 (day 1), vincristine 1.4 mg/m^2 (day 1) and dacarbazine (DTIC) 600 mg/m^2 (days 1 and 2) every 3 weeks as previously proposed by Averbuch et al. [1]. After six cycles there was a minor clinical response. He gained weight and felt better, but there was no significant decrease in urinary VMA excretion. Radiologic studies showed stable disease. Chemotherapy was discontinued. He developed back pain and paresthesias in his left leg 3 months later and evaluation showed progression of his bone metastases and signs of spinal cord compression. He received corticosteroids and palliative radiotherapy.

Chemotherapy was reinitiated with dose-intensive cisplatin 70 mg/m^2 (days 1, 8, 15, 29, 36 and 43) in combination with oral etoposide 50 mg (days 1–15 and 29–43) without evidence of response. After a period of 4 months without any anticancer therapy, he was started with paclitaxel 175 mg/m^2 (3-h infusion) in a 3-weekly schedule because of progression of the osteolytic lesions. After nine courses there was a documented minor response of the abdominal mass as well as of the enlarged lymph nodes on CT scan. He experienced a significant clinical improvement during a period of 1 year. In total, 17 courses of paclitaxel were administered. Urinary VMA excretion decreased from 1238 μmol/24 h to 476 μmol/24 h indicating a partial biochemical response. During the paclitaxel therapy there was no serious toxicity except for alopecia CTC grade 2 and neurotoxicity grade 1 (NCI-CTC scale) [9]. After 1 year of therapy, the disease progressed and paclitaxel was discontinued. Currently, he is participating in a phase I study with a new anticancer therapy while maintaining a good performance status.

Discussion

Extra-adrenal pheochromocytomas (paragangliomas) occur most frequently in the second and third decade with a male predominance. Retroperitoneally located paragangliomas tend to be more aggressive [21]. The clinical course is highly variable among patients. Dissemination to distant organs causes significant morbidity and mortality (5-year survival 44%), but there is no histologic parameter that can predict the metastatic potential and the outcome [12]. The pathologic distinction between benign and malignant disease is not clear. The only absolute criterion for malignancy is the occurrence of tumors/metastases at sites where chromaffin tissue is usually not present. The fundamental approach to localized adrenal and extra-adrenal pheochromocytomas is surgical resection. When surgery is not an option, other therapeutic modalities can be considered as described below. Chronic treatment with α- and β-blocking drugs has been shown to effectively control blood pressure and other manifestations of hormone overproduction [12, 19]. The long-term efficacy of a therapeutic dose of ^{131}I-MIBG in patients with malignant (metastatic) disease must be proven. Objective initial responses have been reported, although many metastatic foci do not concentrate sufficient amounts of this agent to destroy the tumor completely [3, 11, 18].

Chemotherapy

Published information on the use of chemotherapy for malignant extra-adrenal pheochromocytoma is relatively scarce. During the 1970s cyclophosphamide, streptozotocin and doxorubicin were considered to be the most active single agents in the treatment of this neoplasm [4, 5, 10]. During the last 15 years several reports have been presented on different combination chemotherapy regimens, as listed in Table 1. The overview shows that the most promising regimen is a combination of cyclophosphamide, vincristine and dacarbazine (CVD regimen) also used for neuroblastoma. The largest study (14 patients) demonstrated a complete and partial response rate of 57% with a median response duration of 21 months and a biochemical response in 79% of the patients. The regimen is generally well tolerated and the toxicity is mild [1]. The rationale for the CVD regimen is based on the observation that pheochromocytoma and neuroblastoma have several common biologic features. Both tumors arise from tissue of neuroectodermal origin and both produce catecholamines as well as other neurosecretory peptides [8]. This combination chemotherapy has shown activity in patients with neuroblastoma [6]. Second-line treatment with single-agent carboplatin or cisplatin in combination with etoposide can also have some effect [14]. As far as we know the use of paclitaxel for these tumors has not been reported before.

In our patient the administration of paclitaxel resulted in significant clinical improvement, a partial biochemical response and a minor roentgenologic response, which lasted for a period of 1 year. After treatment with ^{131}I-MIBG, CVD regimen, cisplatin and etoposide there was no response of the disease except for a modest clinical response during the first-line chemotherapy, but with paclitaxel a significant improvement was obtained. The choice of this drug in our patient was based on the observation that paclitaxel has a broad antitumor activity and the use of this anticancer agent for neuroendocrine tumors such as (extra-adrenal) pheochromocytoma may be promising. Phase II studies are difficult to conduct for such rare tumors, but are needed to substantiate the drug's activity. In the future it is reasonable to consider paclitaxel as a single agent or in combination with other drugs for the treatment of this advanced neoplasm.

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