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Continued tumor reduction of metastatic pheochromocytoma/paraganglioma harboring succinate dehydrogenase subunit B mutations with cyclical chemotherapy

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Abstract

Patients harboring germline mutations in the succinate dehydrogenase complex subunit B (SDHB) gene present with pheochromocytomas and paragangliomas (PPGL) that are more likely malignant and clinically aggressive. The combination chemotherapy cyclophosphamide, vincristine, and dacarbazine (CVD) was retrospectively evaluated in patients with *SDHB*-associated metastatic PPGL. Twelve metastatic PPGL patients harboring *SDHB* mutations/polymorphisms with undetectable SDHB immunostaining were treated with CVD. CVD therapy consisted of 750 mg/m^2 cyclophosphamide with 1.4 mg/m^2 vincristine on day 1 and 600 mg/m^2 dacarbazine on days 1 and 2, every 21–28 days. Treatment outcome was determined by RECIST criteria as well as determination of response duration and progression-free and overall survivals. A median of 20.5 cycles (range 4–41) were administered. All patients had tumor reduction (12–100% by RECIST). Complete response was seen in two patients, while partial response was observed in 8. The median number of cycles to response was 5.5. Median duration of response was 478 days, with progression-free and overall-survivals of 930 and 1190 days, respectively. Serial [^{18}F]-

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Compliance with Ethical Standards

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical Approval: All procedures performed in studies involving human particpants were in accordance with the ethical standards of the Institutional Review Board of the National Cancer Institute of the National Institutes of Health and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

fluorodeoxyglucose positron emission tomography and computed tomography imaging demonstrated continued incremental reduction in maximal standardized uptake values (SUV_{max}) values in 26/30 lesions. During treatment administration, the median SUV decreased from >25 to <6, indicating the efficacy of chemotherapy over a prolonged period of time. Prolonged therapy results in continued incremental tumor reduction, and is consistent with persistent drug sensitivity. CVD chemotherapy is recommended to be considered part of the initial management in patients with metastatic *SDHB*-related PPGL.

Keywords

Pheochromocytoma/Paraganglioma; Succinate Dehydrogenase; Cyclophosphamide; Vincristine; Dacarbazine

Introduction

Pheochromocytomas and paragangliomas (PPGLs) are rare catecholamine producing neoplasms that arise from chromaffin tissue of the adrenal medulla and the sympathetic or parasympathetic ganglia, respectively. PPGLs occur in 2 to 8 people per million with a peak incidence in the fourth and fifth decades of life [1–4]. Catecholamines (dopamine, norepinephrine, and epinephrine) are a class of neurotransmitters [Eisenhofer 2004]. Hypertension, tachycardia, headache, pallor, sweating, and feelings of anxiety are the most common symptoms associated with catecholamine excess [Zelinka 2007; Lenders 2005], and sustained, uncontrolled catecholamine secretion can lead to severe cardiovascular complications. In 2013, Stolk et al reported that compared to their essential hypertensive counterparts, PPGL patients were 14 times more likely to experience a cardiovascular event due to their prolonged exposure to catecholamines [Stolk 2013]. While surgical anesthesia and tumor manipulation are considered the most direct means of stimulating an eruption of catecholamines, excessive physical activity, traumatic psychological scenarios, certain foods, and medications used to treat nausea, depression, allergies, and infections may likewise elicit an unexpected significant release of catecholamines [Lenders 2005; Pacak 2007]. Even without a trigger, these tumors are capable of producing dangerous levels of catecholamines. Patients presenting with classic signs of catecholamine excess must be appropriately treated with an adrenoceptor blockade in order to achieve control of their blood pressure and heart rate and prevent other organ-specific damage [Agarwal 2011]. However, approximately 20% of patients *do not* display any symptoms related to an abundance of circulating catecholamines due to the downregulation of β-adrenergic receptors found in heart and adipose tissues after prolonged exposure to elevated circulating catecholamines [Tsujimoto 1984]. These patients are too at risk for suffering from cardiovascular catastrophes such as sudden death, myocardial infarction, heart failure, stroke, and shock, and should likewise be medically treated with an alpha adrenoceptor blockade.

Succinate dehydrogenase complex subunit B (*SDHB)*-related PPGLs are predominately norepinephrine and dopamine secreting tumors [Timmers 2007]. In contrast to other hereditary PPGL syndromes, *SDHB* mutation carriers are more likely to present with clinical symptoms and biochemical evidence of elevated metanephrines and the novel

biomarker plasma methoxytyramine, the O-methylated metabolite of dopamine [Zelinka 2007; Eisenhofer 2012]. Additionally, the rate of metastases is much higher in patients with germline *SDHB* mutations [16–22]. Depending on the genetic background and location, 3–36% of PPGLs are metastatic at presentation [13–15]. Although some morphological or histological criteria to distinguish benign from malignant disease has been introduced, the diagnosis of malignancy is often made clinically [7–12]. Mutations in the *SDHB* gene have been found in families with abdominal, pelvic, and thoracic PPGLs. *SDHB* mutation carriers develop disease early in life and are more likely to develop malignant PPGLs as well as additional tumors (renal cell carcinoma, gastrointestinal stromal tumors, and rarely, pituitary tumors) [17–21]. In contrast to sporadic cases where tumors are found outside the adrenal gland less than 40% of the time, *SDHB*-related malignant PPGLs usually present in an extra-adrenal location [22,23]. The most effective treatment for PPGL is surgical resection [24–26]. However, patients with metastatic PPGL have a 5-year survival <50% than their age-matched controls [27,28].

Several single agents and multi-drug regimens have been evaluated in a limited number of patients with variable results. The most active chemotherapy regimen a combination of cyclophosphamide, vincristine, and dacarbazine (CVD) produces remissions of moderate duration in symptomatic patients [27,28,30,31]. An analysis of 18 patients with PPGL treated with CVD and followed for 22 years, showed 2 (11%) complete and 8 (44%) partial responses [27]. All patients with tumors scored as responding reported symptom improvement. CVD was well tolerated with only grade I/II toxicities [27]. Since it is known that patients with PPGL harboring *SDHB* mutations have an earlier presentation of metastatic disease and a worse prognosis, we report the outcome of 12 patients with *SDHB* mutations/polymorphisms or lacking SDHB expression and metastatic PPGL treated with CVD at a single institution. We describe a high response rate to CVD and present evidence of prolonged treatment results in continued tumor reduction. The risk/benefits of continued long-term treatment are also discussed.

METHODS (See also Supplementary Material)

Patients and methods

In August 2005, 12 patients with metastatic PPGL consented to receive chemotherapy. These 12 patients included every patient with metastatic PPGL treated with chemotherapy during this period at our institution. The chemotherapy used, while now considered a “standard option,” had previously been administered on diagnostic and treatment protocols approved by the Institutional Review Board of the National Cancer Institute. All had adequate bone marrow function as well as normal renal and hepatic function with a Karnofsky PS >30%.

Drug therapy and methods

Before starting CVD, drugs were administered to control symptoms of catecholamine excess and to maintain a normal blood pressure and heart rate. Initial treatment consisted of up to 240 mg/day oral of phenoxybenzamine, an α-adrenergic blocker, usually in combination with a β-adrenergic blocker such as propranolol or atenolol. If blood pressure remained

elevated, a calcium channel blocker, or up to 2.0 g/day metyrosine, a catecholamine synthesis inhibitor, was administered. CVD consisted of intravenous cyclophosphamide (750 mg/m^2) and vincristine (1.4 mg/m^2) on day 1, and intravenous dacarbazine (600 mg/m^2) on days 1 and 2, every 21–28 days.

Treatment evaluation and methods

Radiology and nuclear medicine studies were repeated every 6 to 16 weeks. If the original studies were abnormal, the interval varied for the various imaging modalities. Tumor response was based on RECIST [31] and results observed on computed tomography (CT) and/or magnetic resonance imaging (MRI) [29]. [^{18}F]-fluorodeoxyglucose positron emission tomography and computed tomography ([^{18}F]-FDG PET/CT) scans and [$^{123/131}$I]-metaiodobenzylguanidine (MIBG) scintigraphy were not utilized to score responses.

RESULTS

Patient demographics and laboratory data are summarized in Tables 1 and 2. All had a diagnosis of PPGL and evidence of a mutation/polymorphism in the SDHB gene (SDHB expression was not detectable in the patient with a polymorphism) (Figure 1). Initial age of diagnosis was early in life (median 33, range 18–51), all previously underwent surgical resection of original tumors, and 7 of the 12 patients had had at least one metastasectomy. All patients were normotensive at the time of treatment, with 9 requiring blood pressure control via antihypertensive medications.

Chemotherapy with CVD was initiated due to disease burden, location near critical structures (spinal cord), and refractory symptoms of catecholamine excess. In some, this occurred after a period of observation, while in others, CVD was started soon after referral to the National Institutes of Health. A median of 20.5 cycles was administered (range of 4–41). Reductions or delays in vincristine (after median 10 cycles) for peripheral neuropathy and dacarbazine (after median 6 cycles) for delayed/incomplete bone marrow recovery were made in 10/12 patients.

Tumor shrinkage was observed in all patients (12–100% by RECIST) with two complete responses (CR) and eight partial responses (PR) (Figure 2 and Supplementary Figure 1). All responses were confirmed a minimum of four weeks after initially documented. Responses were observed at all sites of disease including the liver, lungs, retroperitoneal nodes, and bones. The median number of cycles to response was 5.5. Median efficacy values included a median duration of response of 478 days (range 127–1623 days), median PFS of 930 days, and median OS of 1190 days.

In our experience [^{18}F]-FDG PET imaging has been very sensitive in detecting metastases in patients with *SDHB* mutations, identifying both visceral as well as osseous sites of disease [32]. Gradual and continued reduction in the standardized uptake values (SUVs) occurred with successive cycles of chemotherapy, the rate of fall varying over time, and amongst various lesions. Figure 3 shows evolution of [^{18}F]-FDG PET images over time. The SUV$_{max}$ values in 26/30 lesions evaluated in six patients who had serial [^{18}F]-FDG PET scans fell from a median SUV >25 to <6 over a median time >825 days, providing evidence of

continued drug efficacy during prolonged administration. These reductions in SUVs were accompanied by reductions in tumor sizes on CT or MRI.

DISCUSSION

We report the results of 12 *SDHB*-related metastatic PPGL patients undergoing treatment with CVD chemotherapy. Previous studies have described the activity of CVD chemotherapy against PPGL and suggested that this treatment be used for cytoreduction and to relieve symptoms [27,29]. In this report, we demonstrate two inter-related phenomena – the marked efficacy of CVD chemotherapy, and the slow emergence of drug resistance as evidenced by the ability to achieve continued, incremental reductions in viable tumor over multiple years. It is important to note that we cannot present a comparison to patients whose tumors do not harbor *SDHB* mutations, as the majority of patients treated during this period of time harbored *SDHB* mutations, which is a reflection of our referral pattern and natural, aggressive clinical course of *SDHB*-related PPGL.

Prior to the availability of [^{18}F]-FDG PET/CT imaging and routine testing for *SDHB* mutation status, we observed a gradual reduction in tumor size as well as serum and urinary metanephrines and catecholamines in patients receiving chemotherapy over several years. These results suggested the effectiveness of continued therapy over time, which was later confirmed by demonstrating a continued decrease in [^{18}F]-FDG PET activity (SUV values) over prolonged time periods – an outcome unlike what is normally observed in most solid tumors. Typically, an effective therapy will result in an initial response, only to be followed by progressive disease in a matter of months. However, the patients in the present report experienced continued reduction in tumor quantity with a median PFS of 930 days (30.6 months) and a median duration of response exceeding 478 days (15.7 months).

Several explanations for continued tumor response can be proposed, including (1) the existence of a large fraction of cells in G_0 that were killed only when they emerged from this quiescent state and began to actively divide; and (2) the existence of cells with stem-like properties whose killing leads to a gradual decline in tumor volume as differentiated offspring die [33,34]. More likely however, continued tumor reduction occurred because resistance was slow to develop. Why resistance develops slowly may be explained if tumors harboring *SDHB* mutations are “genetically simpler” and less likely to harbor intrinsically resistant clone(s). The latter would also explain the high response rate.

All patients in this clinical series presented with advanced malignancy and had few existing therapeutic options. Each presented with multi-focal metastases often including anatomic sites such as vertebrae that required multidisciplinary management, including chemotherapy administration. However, prolonged CVD therapy is not without complications. While some patients tolerated nearly full doses over an extended period of time, gradual reductions in doses were required in the majority of patients as they experienced greater difficulty in recovering normal marrow function. Before receiving CVD, the patient previously required two rounds of radiation, and eventually developed acute myeloid leukemia, which highlights the possibility of this known complication, especially when both alkylating agents and radiation therapy are administered [35,36]. Although she had presumed additional

uncharacterized genetic abnormalities (chronic hydrocephalus requiring stent placement in childhood and bilateral ureteral narrowing unrelated to her PPGL requiring bilateral stents), it was felt chemotherapy contributed to this complication. The standard therapeutic options often available for these patients – palliative radiation therapy and [^{131}I]-MIBG – may also contribute to such long-term complications [36,37].

CONCLUSIONS

In summary, we report a high level of activity of CVD chemotherapy in patients with metastatic PPGL and mutations/polymorphisms in the SDHB gene. Chronic therapy over prolonged periods of time resulted in continued tumor reduction consistent with ongoing drug sensitivity. In patients with difficult clinical presentations who demonstrate tumor reduction when CVD chemotherapy is instituted, consideration can be given to extend their current treatment regimen, while balancing the benefit gained with possible long-term complications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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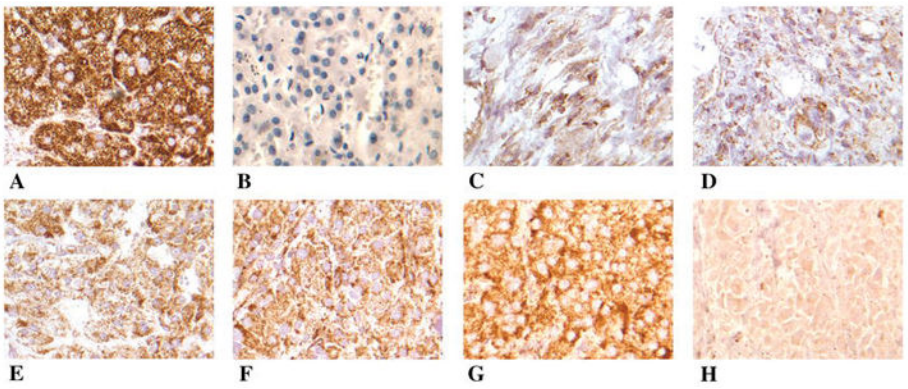

Fig. 1.

SDHB immunostaining of pheochromocytoma and paraganglioma tumors. (A) Positive control; (B) Negative control; (C–G) Tumors staining less (*granular*) than normal control (*clumps*). (H) SNP negative for SDHB.

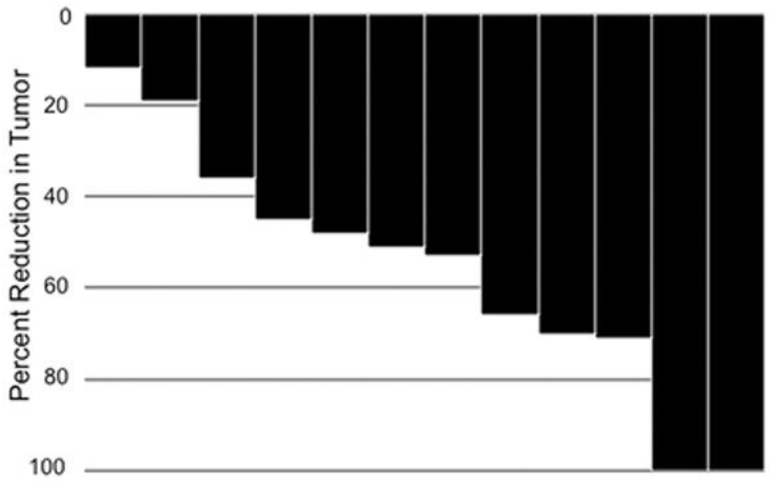

Fig. 2.
Waterfall plot. Waterfall plot depicting response to chemotherapy as assessed by RECIST.

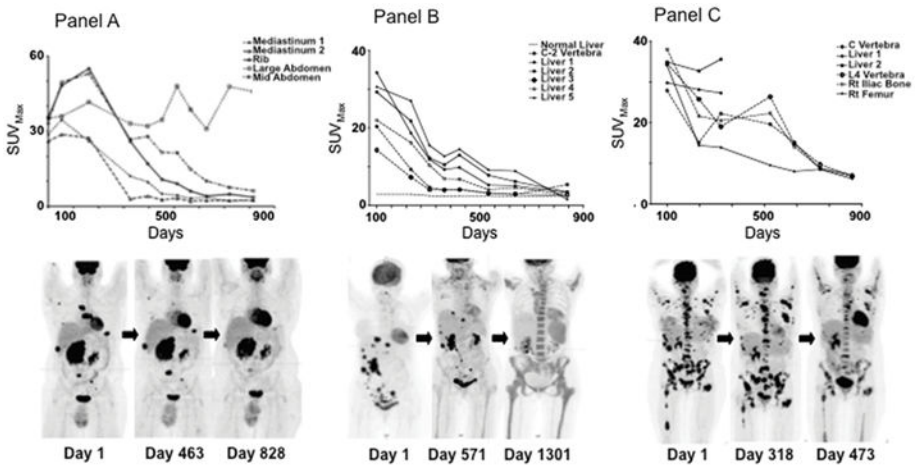

Fig. 3.

[^{18}F]-FDG PET images and gradual reduction in SUV_{max} with chemotherapy in three patients treated with chemotherapy for 600 to 1300 days. Each line depicts the results in an individual lesion. The images on the left (Panel A) depict a patient who had widespread disease that responded to therapy but an abdominal mass that measured nearly 15 cm did not demonstrate much of a change in SUV_{max} despite a 12% reduction in size by RECIST (This is shown as the least response on the Waterfall Plot). [Panel A = Patient #3; Panel B = Patient #8; Panel C = Patient #7]

Table 1

Patient and Tumor Characteristics

	Sex	Age at diagnosis	Age CVD Started	Initial Site of Disease	Sites of Metastasis	Family History	Biochemical Phenotype	BP treatment	Mutation Status			
									Gene	Nucleotide	Amino Acid	Exon
1	F	18	35	Adrenal	Liver, bones	Pancreatic cancer	N	No	SDHB	136 C→T	Arg^{46}→Stop	2
2	M	24	31	Paraspinal (T3-4)	Lung, nodes, spine, bones	Cervical cancer	NEG	No	SDHB	136 C→T	Arg^{46}→Stop	2
3	M	40	42	Renal, paraspinal	Renal, bones, paraspinal, liver	Hodgkin's lymphoma	N	Yes	SDHB	136 C→T	Arg^{46}→Stop	2
4	F	51	52	Retroperitoneum	Lung, spine, bones	No Cancer	N	Yes	SDHB	IVS3+1 G→A	Splice	3
5	M	32	38	Extra-adrenal	Liver, nodes	PHEO	N, D	Yes	SDHB	72+1 G→T	(−)	Intron 1
6	M	27	29	Pelvic	Lung	PHEO	A, N, D	Yes	SDHB	196 C→T	Cys^{66}→Tyr^{66}	(−)
7	F	38	41	Adrenal, tail pancreas	Pelvic bones, spine, liver	No Cancer	NEG	Yes	SDHB	136 C→T	Arg^{46}→Stop	2
8	F	21	25	Adrenal	Liver	No Cancer	N, D	Yes	SDHB polymorphism	487 T→C	Ser^{163}→Pro^{163}	5
9	M	34	35	Retroperitoneum	Nodes	Glomus tumor	N, D	Yes	SDHB	IVS3-1 G→C	Splice	3
10	M	50	50	Adrenal	Peri-aortic nodes, liver	PHEO/PGL	N, D	Yes	SDHB	Deletion	Deletion	1
11	M	37	40	Peri-aortic nodes	Liver	PGL	N, D	Yes	SDHB	590 C→G	Pro^{197}→Arg^{197}	6
12	F	32	41	Adrenal	Chest wall, liver	PGL	N	No	SDHB	Deletion	Deletion	1

Abbreviations: PHEO: Pheochromocytoma; PGL: Paraganglioma; SDHB: Succinate Dehydrogenase Complex Subunit B; IVS: Intervening sequence; A: Adrenergic; D: Dopaminergic; N: Noradrenergic; NEG: Biochemically negative;

Table 2

Prior Therapies, Treatment Summary, and Response Parameters

	Prior Therapies	Total Number of Chemotherapy Cycles	Number of Cycles to PR	Maximum Response [Percent tumor shrinkage]	Duration of Response [Days]	PFS [Days]	OS [Days]
1	XRT, MIBG	22	20	48%	142	623	>763
2	XRT, RFA	32	18	70%	529	949	1461+
3	XRT	26	Not achieved	12%	(−)	1369	2337
4	Octreotide LAR	8	Not achieved	19%	(−)	1019	1349
5	Bevacizumab	24	6	100%	1623+[a]	1734+[A]	1796+[a]
6	None	7	2	66%	>127[b]	>175[b]	870
7	Carboplatin + Paclitaxel	26	11	45%	578	910	1032+
8	XRT	41	5	71%	1561	1632[c]	1632
9	XRT	4	2	36%	176	337	513
10	None	11	2	53%	245	327	532+
11	RFA	26	3	100%	427	615	615+
12	XRT	19	14	51%	796	1636	>1636[d]
	Median	**20.5**	**5.5**	**52%**	**478**	**930**	**1190**

[a] Continues in complete remission

[b] Achieved partial response but did not return for follow up after 175 days. Still in PR at 175 days

[c] In PR when last evaluated; died of acute myeloid leukemia

[d] Died in Mexico, date uncertain

Abbreviations: XRT: Radiation therapy; RFA: Radiofrequency ablation; PR: Partial response; PFS: Progression-free survival; OS: Overall survival