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Lenvatinib as a Therapeutic Option in Unresectable Metastatic Pheochromocytoma and Paragangliomas

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Abstract

Context: Metastatic pheochromocytomas and paragangliomas (mPPGL) are rare vascular neuroendocrine tumors that highly express vascular growth factors. Systemic treatment options in cases of unresectable multisite disease are limited. Multikinase inhibitors that inhibit angiogenesis, such as lenvatinib, have proven effective in several other malignancies, and may be a viable option for mPPGL.

Objective: We aimed to evaluate the efficacy of lenvatinib as salvage therapy in mPPGLs.

Methods: This was a retrospective analysis of mPPGL patients ≥ 18 years of age who received lenvatinib from 2015 to 2020 at a tertiary referral center. Patients were started on lenvatinib 20 mg daily and dose was adjusted according to tolerance or disease progression.

Results: Eleven patients were included. Median treatment duration was 14.7 months (95% CI, 2.3-NE). Treatment was discontinued due to disease progression, adverse events, or death. Overall survival at 12 months was 80.8% (95% CI, 42.3-94.9%) but its median was not reached. Median progression-free survival was 14.7 months (95% CI, 1.7-NE). Among the 8 patients with measurable disease, overall response rate was 63%, as 5/8 experienced a partial response and 3/8 had stable disease. Worsening hypertension and anemia were the most common adverse events.

Conclusion: Lenvatinib may be a viable treatment option for mPPGL, although at the potential risk of worsening hypertension. Larger, multicenter studies are needed to better characterize treatment efficacy.

Key Words: pheochromocytoma, paraganglioma, multikinase inhibitor, cancer

Abbreviations: AE, adverse event; CVD, cyclophosphamide, vincristine, and dacarbazine; ECOG, Eastern Cooperative Oncology Group; MKI, multitargeted kinase inhibitor; mPPGL, metastatic pheochromocytoma/paraganglioma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PPGL, pheochromocytoma/paraganglioma; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SDH, succinate dehydrogenase; VEGF, vascular endothelial growth factor.

Pheochromocytomas and paragangliomas (PPGL) are chromaffin cell tumors that arise from the adrenal medulla and from parasympathetic and sympathetic ganglia, respectively [1]. Because both tumors arise from chromaffin cells, they share many common characteristics and treatment strategies. Although these tumors are usually nonmetastatic, 15% to 17% are metastatic [2]. Patients harboring succinate dehydrogenase (SDH) subunit B mutation are more likely to develop metastatic disease [3, 4]. In general, the 5-year mortality rate for metastatic PPGL (mPPGL) is 37% (95% CI, 24%-51%) [5].

First-line treatment is surgical resection of the primary lesion(s) and/or isolated metastatic lesion(s). Systemic management for multisite disease burden includes metaiodobenzylguanidine labeled with iodine 131 (^{131}I-MIBG), DOTATATE labeled with lutetium 177 (^{177}Lu-DOTATATE), kinase inhibitors, or chemotherapy for multisite disease burden [6], with MIBG being the only approved systemic option [7]. Cytotoxic chemotherapy, traditionally cyclophosphamide, vincristine, and dacarbazine (CVD), has long been utilized for mPPGL, where partial or complete response rates varied from 44% to 100% [8-10]. However, this wide disparity can be explained by differences in patient population and protocols/duration of treatment employed.

In general, mPPGL are very vascular tumors due to high growth factor expression promoting angiogenesis. The most common of these angiogenic growth factors is vascular endothelium growth factor (VEGF) [11]; however other angiogenic factors also exist. Certain hereditary conditions, especially those with the SDHB mutations or other SDH mutations involving subunits A, C, D, and co-factor SDHAF2 (SDHx) may further promote tumor vascularity [12]. These mutations inactivate the SDH enzyme, leading to an accumulation of succinate and consequently inducing a pseudohypoxic state; this, in turn, increases the expression of VEGF and other angiogenic factors [13-17]. Other hereditary conditions linked

to PPGL, especially von Hippel-Lindau (VHL) syndrome, have a similar molecular background [18, 19].

Multitargeted kinase inhibitors (MKI), specifically those inhibiting angiogenesis, have appropriately been investigated for therapy in mPPGL. Sunitinib and pazopanib, for example, have been studied for this indication with some success [20-22]. Lenvatinib is a broad coverage MKI that is currently approved and highly effective in the treatment of advanced thyroid, renal, hepatic, and endometrial carcinoma. It has already been trialed in a single patient with SDHB(+) mPPGL and was noted to have significant reduction in tumor burden [23]. We hypothesized that lenvatinib may also be effective as a therapeutic option in mPPGL. Herein we describe a prospective phase 2 study and a retrospective mPPGL case cohort treated with lenvatinib.

Methods

Study Objectives

Metastatic PPGL is defined as the presence of chromaffin cells where these cells should not exist, or invasion of the PPGL into local tissue [24]. The primary objective was to determine the overall response rate (ORR), defined as the percentage of patients who had a partial response (PR) or complete response to lenvatinib in patients with mPPGL. Secondary objectives were to determine overall survival (OS), progression-free survival (PFS), and duration of response.

Study Design and Participants

This was initially a phase 2 prospective study (NCT03008369) analyzing patients who received lenvatinib for mPPGL. However, due to slow accrual rate, the trial was terminated. Hence, the non-trial patients treated with lenvatinib were reviewed retrospectively. This study was approved by the Mayo Clinic Institutional Review Board. We searched our hospital medical records from 2015 to 2020 to identify patients with mPPGL treated with lenvatinib. Patients with confirmed mPPGL were included if they met the following criteria: ≥ 18 years of age, disease not amenable to localized treatments, Eastern Cooperative Oncology Group (ECOG) performance status < 2, life expectancy > 24 weeks, normal liver and kidney function, and well-controlled blood pressure.

Exclusion criteria included: additional unrelated primary malignancy within the past 2 years, other PPGL treatment modalities ≤ 21 days prior to start of drug, poor tolerance to other treatments, advanced or untreated cardiovascular disease, known active and/or untreated brain metastases, prior use of lenvatinib, high risk for gastrointestinal perforation, ongoing treatment of thrombotic event, active infection, pregnant or nursing women, and men or women of childbearing potential who were unwilling to use contraception.

Patients in the prospective study were eligible only if they had measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria [6]. Other non-trial patients could have nonmeasurable disease such as bone metastasis, pleural effusion, or lymph nodes < 1.5 cm.

Patients were started on lenvatinib 20 mg daily, the dose was adjusted based on the criteria outlined in the protocol. Dose was held or reduced based on degree of adverse events, generally if grade ≥ 2 or 3. Cycle of treatment was defined as every 28 days. Parameters collected included baseline demographics, germline or somatic mutational status (screening for SDHx, RET, VHL, NF1), previous treatment modalities (ie, surgery, chemotherapy, radiotherapy, ^{131}I-MIBG, or MKI), number of completed cycles, hormonal response. The adverse events (AEs) were graded based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.

Statistical Analysis

Patient demographic information was summarized using descriptive analysis. Response to lenvatinib was based off of RECIST 1.1 criteria. Kaplan-Meier curves were used to assess OS, PFS, and treatment duration. OS was defined as length of time patients remained alive after starting lenvatinib. PFS was defined as length of time from drug initiation until date of first disease progression or death. SAS version 9.4 software was used to calculate the statistical data.

Results

We identified 11 patients with mPPGL who met inclusion criteria, and their baseline characteristics prior to starting lenvatinib are outlined in Table 1. Seven (63%) were male, and average age was 56 years (range, 44-69 years). No patient had an additional preexisting primary malignancy of a different organ. Most patients' primary tumor involved a paraganglioma (82%) and most were located in the abdomen (73%); other primary sites of disease included the neck, chest, and bladder with 1 person each. Seven (63%) had secretory disease, 5/11 (45%) had a germline mutation (all involving SDHB, though specific sequence alteration was not reported). Due to small numbers and other confounding variables, differences between SDHB-mutated and wild-type were not analyzed.

All but 1 patient had previously undergone surgery to remove the primary tumor; there was complete resection (R0) in 8/10 patients. The most common site of metastasis was to lymph nodes and/or bone (90.9%), followed by liver and peritoneum (54.5%), lung (45.5%), bladder and recurrent disease within the postsurgical adrenal bed (18.2%), and paravaginal (9.1%). Seven patients previously received radiotherapy. Five patients had received MIBG treatment previously. All patients received prior cytotoxic chemotherapy in the form of cyclophosphamide, vincristine, and dacarbazine, plus or minus octreotide. Only 2 patients were previously treated with an MKI, both treated with pazopanib. Most patients had bony involvement and received bone modulating therapy (zoledronic acid or denosumab). The ECOG status was primarily 0 or 1.

Of the 11 patients, 8 had measurable disease. Among the 8 patients, the ORR was 63%. Five patients demonstrated a PR to lenvatinib, and 3 patients had stable disease. There were no complete responses. The remaining 3 had unmeasurable disease though had less avidity on PET (Fig. 1). Data on biochemical response was not available for all patients, although there was a trend in overall reduction of metanephrines/normetanephrines.

At 12 months, 58.4% (95% CI, 22.7%-82.3%) of patients remained on treatment; median treatment duration was 14.7 months (95% CI, 2.3-NE) (Fig. 2). The OS at 12 months was 80.8% (95% CI, 42.3%-94.9%) but median OS was not reached (Fig. 3). Median PFS was 14.7 months (95% CI, 1.7-NE); PFS was 71.6% (95% CI, 35%-89.9%) at 6 months and 61.4% (95% CI, 26.6%-83.5%) at 12 months (Fig. 4).

Table 1. Baseline demographics

Parameter	Number of patients (% of 11 total patients)
Gender	
Male	7 (64%)
Female	4 (36%)
Diagnosis	
Pheochromocytoma	2 (18%)
Paraganglioma	9 (82%)
Secretory	
No	4 (36%)
Yes	7 (64%)
Inherited syndrome	
No	6 (55%)
Yes	5[a] (45%)
Primary site	
Neck	1 (9%)
Chest	1 (9%)
Abdomen	8 (73%)
Bladder	1 (9%)
Previous surgery	
No	1 (9%)
Yes	10 (91%)
Surgical approach	
Primary tumor resection	10 (91%)
Biopsy only	1 (9%)
Status of primary tumor after surgery	
No residual tumor	8 (73%)
Resected, residual tumor	2 (18%)
Unresected	1 (9%)
Recurrence at primary site	
No	3 (27%)
Yes	8 (73%)
Site(s) of metastatic disease	
Node	10 (91%)
Liver	6 (55%)
Adrenal bed	1 (9%)
Kidney	2 (18%)
Peritoneum	6 (55%)
Bone	10 (91%)
Lung	5 (45%)
Bladder	2 (18%)
Paravaginal	1 (9%)
Previous radiotherapy	
No	4 (36%)
Yes	7 (64%)
Type of prior radiotherapy	
EBRT	6 (55%)
IMRT	1 (9%)
MIBG uptake	
Negative	2 (18%)
Positive	5 (46%)
NA	4 (36%)
Prior use of CVD	
Yes	11 (100%)

Table 1. Continued

Parameter	Number of patients (% of 11 total patients)
+octreotide	3 (27%)
Previous MKI	
No	9 (82%)
Yes	2[b] (18%)
Bone modulating therapy	
No	3 (27%)
Yes	8 (73%)
Best response to all prior treatments	
Partial response	6 (55%)
Complete response	5 (45%)
Performance status	
0	4 (36%)
1	6 (55%)
2	1 (9%)

Abbreviations: CVD, cyclophosphamide, vincristine, dacarbazine; EBRT, external beam radiation, IMRT, intensity modulated radiation therapy; MIBG, metaiodobenzylguanidine; MKI, multitargeted kinase inhibitor; NA, data not available.
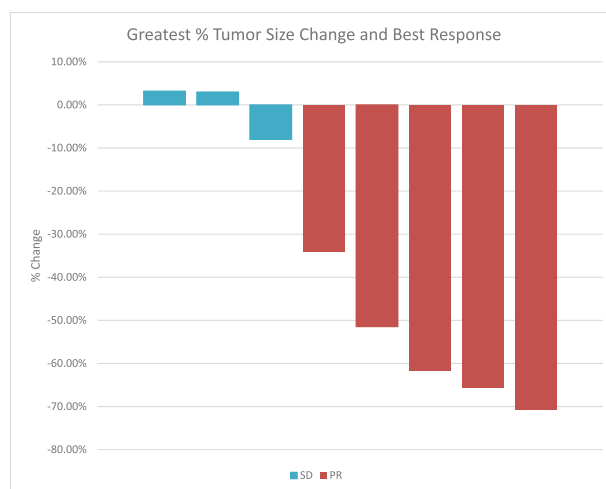[a]All SDHB.
[b]Both pazopanib.

Figure 1. Change in tumor size. Out of 11 patients, 8 had measurable disease. 5/8 achieved a partial response (PR), and 3 patients had stable disease (SD), defined by RECIST 1.1.

All but 1 patient required a dose reduction. As expected, the most common AE was hypertension, as seen in 9/11 patients, and required adjustment of their antihypertensive therapy. Other side effects, as seen with other VEGF inhibitors, included anemia, fatigue, cough, proteinuria, nausea, vomiting, and weight loss. Our population did not develop oral mucositis or dysesthesia, or palmar-plantar erythrodysesthesia syndrome. There were 7 patients on thyroid hormone replacement who required dose adjustment while on lenvatinib. Treatment was discontinued due to disease progression (4/11), AEs (2/11) and death (1/11), although the latter was attributed to disease progression. The remaining 3 patients continued therapy through their last follow-up.
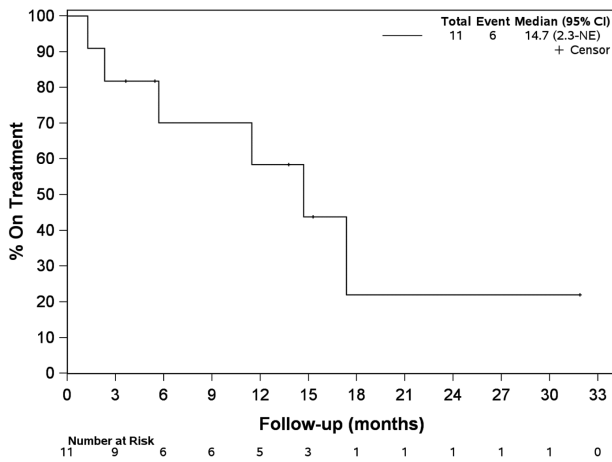
Figure 2. Median treatment duration. Median time from initiation of lenvatinib to discontinuation or date of last follow-up was 14.7 months.

Figure 3. Overall survival. Overall survival was not reached.

Discussion

Pheochromocytomas and paragangliomas are highly vascular tumors and their growth is promoted by this increased blood supply. For focal disease, treatment options include surgery, ablation, and radiation; however, the treatment for inoperable, multisite disease remains a challenge, especially given the rarity of this neuroendocrine malignancy. Systemic options have included nuclear medicine–based therapies, such as ^{131}I-MIBG (Azedra) and ^{177}Lu-DOTATATE, although time to maximal response may be delayed after initial treatment or reduced number and degree of PR [7, 25].

Cytotoxic chemotherapeutic options have traditionally involved cyclophosphamide, vincristine, and dacarbazine. This combination has shown an ORR of 57% to 100% [8-10, 26] and 72% to 79% of patients among 2 studies experienced a complete or partial biochemical response [8, 9]. Response duration was 1 to 2 years, although patients experienced hematologic, neurologic, and gastrointestinal side effects [8-10].

MKIs also remain as an effective treatment strategy against several malignancies as they targets angiogenesis. In mPPGL, there is a significantly higher expression of VEGF, which accounts for the tumor's high vascularity and subsequent growth [11]. Given the high expression of VEGF in mPPGL and its role in tumor growth, MKIs have been a viable option to treat these tumors.

The MKI lenvatinib broadly inhibits various receptor targets both on the tumor as well as its vascular supply. Among these targets include VEGF, fibroblast growth factor, and platelet-derived growth factor receptors, which are regulators of angiogenesis, as well as RET and KIT, which are directly expressed on tumors. Through these mechanisms, lenvatinib has been effective in treating other malignancies. Our study has also shown promising outcomes, including a prolonged median PFS of 14.7 months as well as an ORR of 63% among those with measurable disease. Although head-to-head comparison between lenvatinib, sunitinib, or pazopanib could not be achieved due to differences in study design, ORR and PFS may be higher in the lenvatinib-treated population.

In a retrospective analysis of 17 patients who received sunitinib, median PFS was 4.1 months and ORR was 57% (8 of the 14 assessable patients); progressive disease occurred in 6 patients. There was also some improvement in other clinical parameters, including overall blood pressure, and it was noted that patients with an SDHB mutation saw a
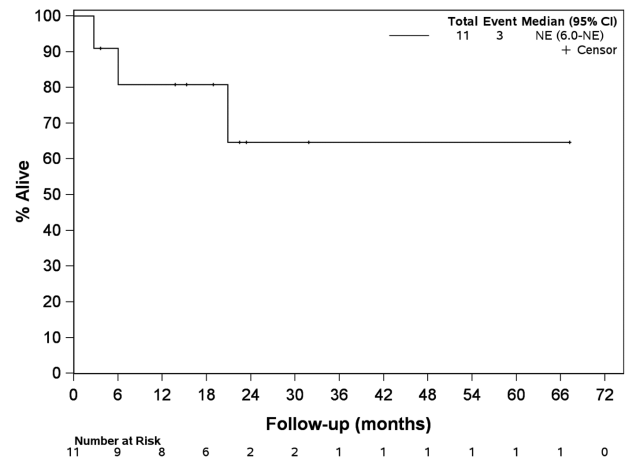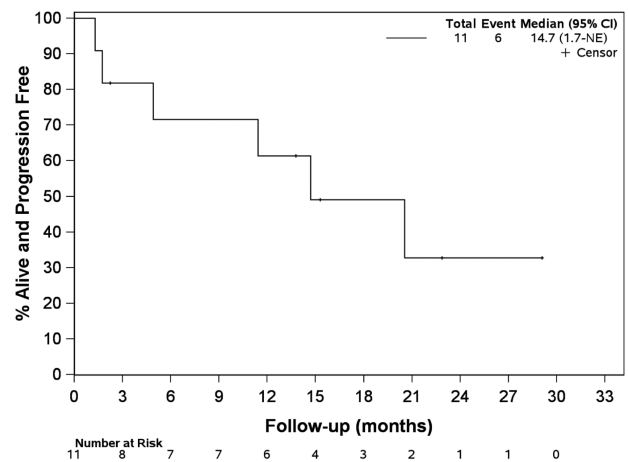

Figure 4. Progression-free survival. Median progression-free survival was 14.7 months.

benefit [20]. Sunitinib was also evaluated in a phase II open label trial, where 23 of the evaluable patients had a median PFS of 13.4 (95% CI, 5.3-24.6) months; the ORR was 13%. Similar to our study, the OS end point was not reached [22]. Currently, a multicenter randomized controlled phase II study assessing efficacy of sunitinib on PFS of mPPGL is underway (NCT01371201), in which preliminary results have shown a median PFS of 8.9 months (95% CI, 5.5-12.7) in the sunitinib group vs 3.6 months (95% CI, 3.1-6.1) in the placebo group [27]. Pazopanib was also assessed in a phase II open label prospective trial; however, due to poor accrual rate, the study was discontinued. Of the 6 enrolled and evaluable patients, median PFS was 6.5 months and OS was 14.8 months, suggesting some clinical efficacy; however, only 1 patient experienced a PR [21].

Hypertension remains the most common side effect of all MKIs, particularly for lenvatinib as it inhibits multiple sites of angiogenesis, and this a potential limiting factor when treating secretory mPPGL. While hypertension may be more challenging to manage at the initiation of drug therapy, as time passes and if disease and biochemical regression occur, then the number of antihypertensive medications needed should decline. Therefore, it is important that all patients have well-controlled blood pressure prior to initiating an MKI and patients need close follow-up throughout their treatment course.

Additional AEs, such as hematologic and gastrointestinal, and other generalized symptoms, such as fatigue and weight loss, are shared by all MKIs.

The study was limited by its combination of prospective and retrospective cohorts and sample size. We also did not have data on pre- and post-therapy biochemical levels, that is, metanephrines/normetanephrines in all of the patients; hence, these could not be used as a surrogate tumor marker for response in our cohort. Additional data, such as tracking quality of life before and during lenvatinib therapy are lacking. We were unable to conclude whether exposure to a prior MKI impacted response in our population due to small sample size. However, in other tumor populations, lenvatinib continued to show activity in spite of prior exposure to other VEGF inhibitors [28, 29].

Conclusion

Our retrospective analysis demonstrated the efficacy of lenvatinib in mPPGL and shows that it may be a viable option to consider in salvage settings in mPPGL patients. Prospective multicenter studies with a larger sample size are needed to confirm the utility of lenvatinib in the treatment of mPPGL.

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Disclosures

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Data Availability

All data generated or analyzed during this study are included in this published article.

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