



The efficacy of everolimus and sunitinib in patients with sporadic or germline mutated metastatic pancreatic neuroendocrine tumors

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Background: Hyperactivation of mTOR pathway and angiogenesis have been implicated in the pathogenesis of neuroendocrine tumors (NETs). Everolimus, an oral inhibitor of mTOR, and sunitinib, an antiangiogenic drug, are effective targeted therapies approved to treat locally advanced/metastatic pancreatic neuroendocrine tumors (pNETs). Most pNETs are sporadic and mutations in genes involved directly or indirectly in mTOR pathway regulation have been implicated, including somatic mutation in *MEN1* in 44% of cases. About 10% of pNETs can be part of hereditary syndromes, e.g., multiple endocrine neoplasia type 1 (*MEN1*) and Von-Hippel Lindau (*VHL*), and these patients are underrepresented in pivotal phase III trials. We hypothesized that everolimus would be particularly effective in patients with *MEN1*-associated pNETs. Likewise, we inferred that sunitinib would also be beneficial to patients with *VHL*-associated pNETs.

Methods: We conducted a multicenter retrospective and comparative study to assess the efficacy of everolimus and/or sunitinib in a cohort of patients with advanced pNETs with or without known *MEN1* or *VHL* syndrome. The evaluation of the germline mutational status of *VHL* and *MEN1* genes was retrospectively collected from the medical records. The primary endpoints were progression free survival (PFS) and time to treatment failure (TTF) of patients who received at least one month of sunitinib or everolimus in monotherapy.

Results: Thirty-three patients were identified from September 2009 to April 2018. Most were male 60.6%. Median Ki67 was 9%, liver metastases were present in 97%. The majority of tumors were non-functioning. Thirty-one patients received everolimus, of them 8 patients had germline mutations (6 in *MEN1* and 2 in *VHL* genes). Nine patients received sunitinib, of them 3 had germline mutation (2 in *MEN1* and 1 in *VHL* genes). In a median follow up of 26 months, among everolimus-treated patients, mTTF and mPFS were numerically superior in patients with germline mutations compared with those with sporadic pNETs (mTTF: 16.1 vs. 9.9 months, $P=0.888$; mPFS: 33.1 vs. 12.3 months, $P=0.383$). The disease control rate with everolimus was numerically higher in favor of germline mutated tumors compared to sporadic ones (87.5% vs. 68.4%). Sunitinib was used by 1 patient with *VHL* syndrome, achieving a PFS of 17.6 months. In the subgroup of sporadic pNETs, sunitinib was used by 6 patients reaching a mPFS of 18 months (range, 5–25 months), predominantly in second line.

Conclusions: Our study suggests that everolimus may offer a prolonged tumor control in pNETs with germline mutations (*MEN1* or *VHL*) compared to sporadic ones. The small number of patients and the retrospective nature of this study precludes any definitive conclusions.

Keywords: Neuroendocrine; germline mutation; everolimus; sunitinib; pancreatic net

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Introduction

Neuroendocrine tumors (NETs) account for less than 1% of all human cancer cases, affecting about 6 individuals per 100,000 per year in Europe (1). NETs have been reported in almost all organs of the body because they derive from neuroendocrine stem cells, distributed during embryogenesis throughout the neural crest, endocrine glands and diffuse endocrine system. Although they are mostly sporadic, approximately 10% can occur as part of hereditary syndromes, mainly multiple endocrine neoplasia type 1 (MEN1) and Von-Hippel Lindau syndrome (VHL) (2).

The MEN1 syndrome is autosomal dominant, with a prevalence of 2–3 per 100,000, being one of the most common familial cancer syndromes (3). While 30–80% of MEN1 patients develop pancreatic NETs (pNETs), other commonly associated tumors are adenomas of the pituitary gland and duodenum gastrinomas (3-5). In MEN1 patients, pNETs are often nonfunctional (3,4). Importantly, pNETs are the main cause of death among patients with MEN1, with a specific disease survival rate at 10 years ranging between 23% and 62% (6-8). In patients with VHL syndrome, pNETs develop in 10% to 17% and are almost exclusively nonfunctional (9-11). In addition to pancreatic neoplasms, VHL patients often develop a variety of benign and malignant neoplasms, including clear cell renal carcinomas, pheochromocytomas, paragangliomas, hemangioblastomas, retinal angiomas, middle ear endolymphatic sac tumors and papillary cystadenomas of the epididymis and the broad ligament (12,13).

These cancer predisposition syndromes are characterized by deleterious germline mutations in genes that increase tumor susceptibility in the pancreas and other neuroendocrine organs, leading to the development of multiple tumors. However, in sporadic pNETs, the genetic changes involved in neuroendocrine tumorigenesis in the pancreas have just started to be elucidated. Jiao *et al.* performed complete exome sequencing in a set of 10 cases of sporadic pNETs (primary tumor samples) and subsequently the most commonly mutated genes were analyzed in a validation set of 58 pNETs samples. Interestingly, they

found that 44% of the tumors had somatic inactivation mutations in *MEN1*, 43% in *ATRX* and mutations in genes encoding proteins in the mTOR pathway were found in 14% of cases (14). Given that mutations in *MEN1* lead to mTOR hyperactivation (15), it is intuitive to think that mTOR inhibition would be particularly effective in patients with MEN1 syndrome (16). Likewise, there is a rationale to infer that sunitinib, an antiangiogenic agent, would be also beneficial to patients with VHL-associated pNETs. However, to our knowledge, NET patients with such genetic syndromes have been under represented in pivotal phase III trials of sunitinib or everolimus. Therefore, aimed to evaluate the efficacy results of everolimus and sunitinib in patients with pNETs with and without MEN1 or VHL syndromes.

Methods

Study design

We conducted a multicenter retrospective and comparative study to assess the efficacy of everolimus and/or sunitinib in a cohort of patients with advanced pNETs with or without known MEN1 or VHL syndrome. Eligible patients had histological diagnosis of well differentiated NET of pancreatic origin, locally advanced unresectable or metastatic disease and received at least one month of sunitinib or everolimus in monotherapy. The evaluation of the germline mutational status of *VHL* and *MEN1* was retrospectively collected from the medical records and their testing followed standard guidelines for screening based on clinical suspicion. All pNET patients were consecutively selected through an administrative list from one center (A.C. Camargo Cancer Center, Sao Paulo, Brazil) from September 2009 to April 2018; because of its rarity, we also included patients with a genetic diagnosis of VHL- and MEN1-associated metastatic pNET from other three centers in Brazil. The following clinical data were collected: sex, age at onset of targeted therapy, cell differentiation, ki-67 index, metastatic sites, and treatment outcomes.

The study was conducted in accordance with the protocol,

Table 1 Patient characteristics (N=33)

Variable	Value
Gender, n (%)	
Female	13 (39.4)
Male	20 (60.6)
Age, years, median [range]	51 [24–83]
Associated genetic syndrome, n (%)	
None	24 (72.7)
MEN1	7 (21.2)
VHL	2 (6.1)
Location, n (%)	
Head or uncinated process	2 (6.1)
Neck	1 (3.0)
Body or tail	25 (75.8)
Unknown	5 (15.2)
Differentiation, n (%)	
Well-differentiated	20 (60.6)
Poorly-differentiated	1 (3.0)
Neuroendocrine carcinoma	4 (12.1)
Unknown	8 (24.2)
Histological grade, n (%)	
1	4 (12.1)
2	19 (57.6)
3	6 (18.2)
Unknown	4 (12.1)
Ki-67, %, median [range]	9 [1–70]
Hepatic metastasis, n (%)	
Yes	32 (97.0)
No	1 (3.0)
Functionality, n (%)	
Non-functioning	27 (81.8)
Insulinoma	2 (6.1)
Gastrinoma	2 (6.1)
Glucagonoma	2 (6.1)
Follow-up from diagnosis, months, median [range]	26 [2–106]

MEN1, multiple endocrine neoplasia type 1; VHL, Von Hippel Lindau; y, years; m, months.

Good Clinical Practice guidelines of the International Conference on Harmonization (ICH GCP) and applicable local laws and regulatory requirements, and was approved by the Research Ethical Committees.

The primary endpoints were progression free survival (PFS) and time to treatment failure (TTF) of each group. PFS was defined as the time between the first dose of everolimus/sunitinib and discontinuation for disease progression or death. Progression was defined as per the oncologists evaluation as documented in the medical charts. TTF was defined as the time between the first dose of everolimus/sunitinib and discontinuation for any reason, including disease progression, treatment toxicity, patient preference or death. If no event has occurred, the date of the last evaluation was censored.

Descriptive statistics techniques were used to calculate measures such as mean, median and standard deviations of the demographic characteristics of the studied population. The *t*-test of independent samples for continuous variables and Pearson's Chi-square test or Fisher's Exact for categorical variables were used for comparisons between group variables (pNET germline mutated and sporadic). The Kaplan-Meier method was used to calculate the survival curves and they were compared using the log-rank test. For all analyzes, we considered the level of statistical significance of 5% (P value of baseline <0.05). In view of the rarity of the disease under study, the sample size was convenience-based, without a formal calculation.

Results

From September 2009 to April 2018, 33 patients were identified. *Table 1* summarizes the characteristics of the patients. Their median age was 51 years (range, 24–83 years), and the female/male ratio was 39.4%/60.6%. The median Ki-67 was 9% (range, 1–70%), 32 (97.0%) presented liver metastases and 7 (21.2%) patients had bone metastases. The majority of tumors were non-functioning

Out of 33 patients, 31 received everolimus, mostly in first and second lines (38.7% and 25.8%, respectively), of them, 23 were sporadic and 8 had germline mutations (6 in *MEN1* and 2 in *VHL* genes). Nine patients received sunitinib—7 patients received both drugs. Out of the 9 patients that received sunitinib, 6 were sporadic and 3 had germline mutations (2 in *MEN1* and 1 in *VHL* genes).

In a median follow up of 26 months, among 31 everolimus-treated patients, the median TTF (mTTF) and

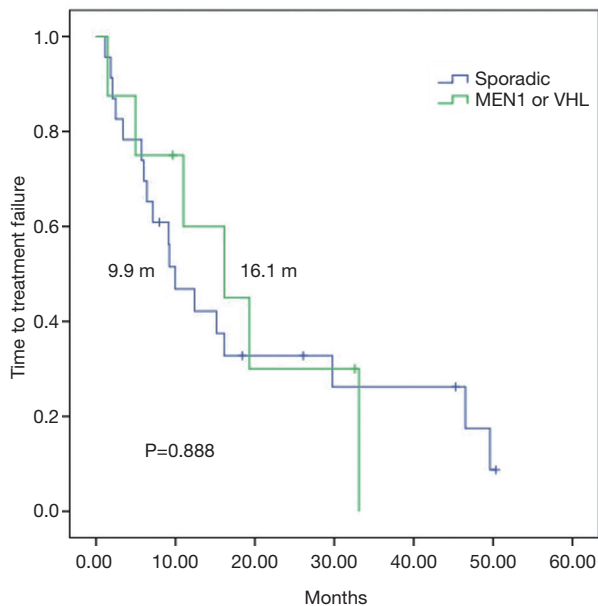


Figure 1 Median time to treatment failure after treatment with everolimus in relation to the presence or absence of genetic syndrome (MEN1 or VHL). MEN1, Multiple Endocrine Neoplasia type 1; VHL, Von-Hippel Lindau; m, months.

median PFS (mPFS) from initiation of everolimus was 12.3 and 15.1 months respectively. The mTTF was numerically superior in patients with germline mutations in *MEN1* or *VHL* compared with those with sporadic pNETs (16.1 vs. 9.9 months respectively; $P=0.888$) (Figure 1). The mPFS was also numerically superior among germline mutated pNETs (33.1 vs. 12.3 months respectively; $P=0.383$) (Figure 2). Patients receiving everolimus in first line showed numerically better mTTF compared with later lines (16.1 vs. 9.2 months respectively; $P=0.392$); this was also observed in mPFS (33.1 vs. 11 months respectively; $P=0.138$).

To control for imbalances between the groups and to analyze a more homogenous sample, performed a subgroup analysis of patients with grade 1–2 sporadic or MEN1-associated pNETs, since G3 tumors in the sporadic group could lead to worse outcomes in this group, The mTTF was similar in patients with or without MEN-1 syndrome (16.1 vs. 15.1 months respectively; $P=0.982$) (Figure 3), whereas mPFS was numerically superior among patients with MEN1 syndrome (33.1 vs. 15.1 months respectively; $P=0.335$) (Figure 4).

Disease control with everolimus [DC = complete response (CR) + partial response (PR) + stable disease (SD)] was observed in 74.1%, whereas 25.9% had upfront

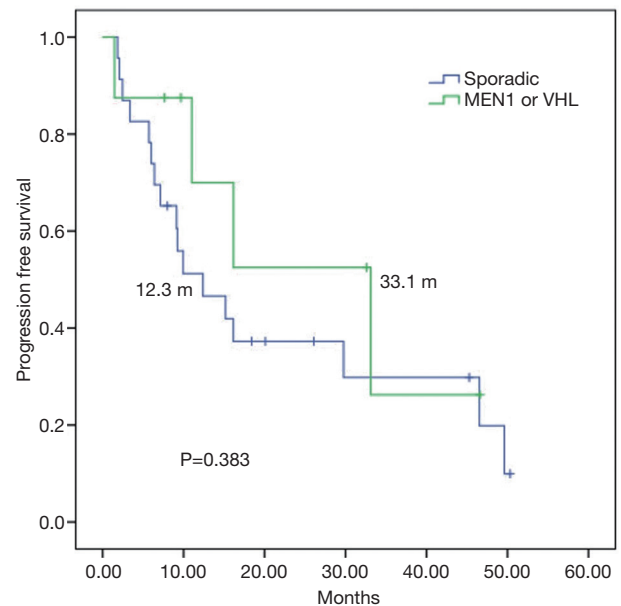


Figure 2 Median progression free survival after treatment with everolimus in relation to the presence or absence of genetic syndrome (MEN1 or VHL). MEN1, Multiple Endocrine Neoplasia type 1; VHL, Von-Hippel Lindau; m, months.

progressive disease (PD). If we separate these findings by sporadic vs. germline mutated pNETs, we obtained DC in 68.4% vs. 87.5% and upfront PD in 31.6% vs. 12.5%, respectively. The reasons for interruption were PD in 20 patients (83.3%), adverse events in 3 patients (12.5%); and others (physician's choice) in 1 patient (4.2%).

Sunitinib was used by one patient with VHL syndrome in second line, achieving a PFS of 17.6 months. Other two patients with MEN1 syndrome used sunitinib with PFS of 1.3 and 2.9 months in second and fifth line, respectively. In the subgroup of sporadic pNETs, sunitinib was used by 6 patients reaching a mPFS of 18 months (range, 5–25 months), predominantly in second line.

Discussion

Although not statistically significant, we observed prolonged mPFS and mTTF, and superior DC in patients with MEN1 or VHL-associated pNETs treated with everolimus. The number of patients who received sunitinib was too small to reach any conclusion.

Studies show that approximately 80% of non-functional pNETs are detected when the disease is already unresectable, often with liver metastases. The 5-year

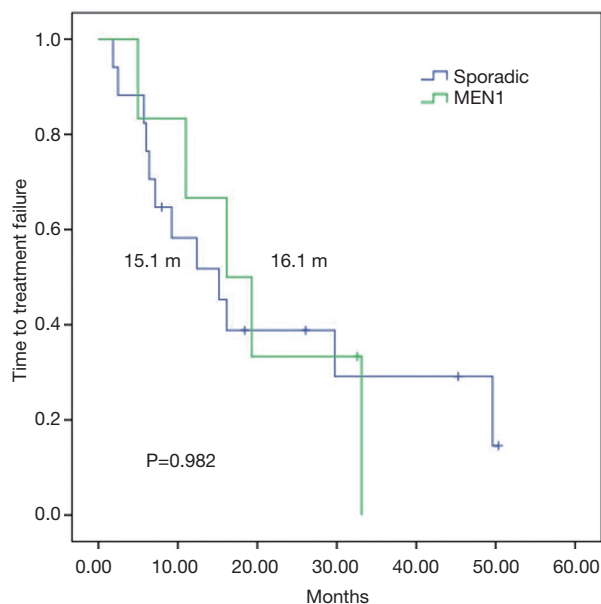


Figure 3 Median time to treatment failure after treatment with Everolimus in relation to the presence or absence of MEN1 in patients with pancreatic NETs grade 1–2. MEN1, multiple endocrine neoplasia type 1; NETs, neuroendocrine tumors; m, months.

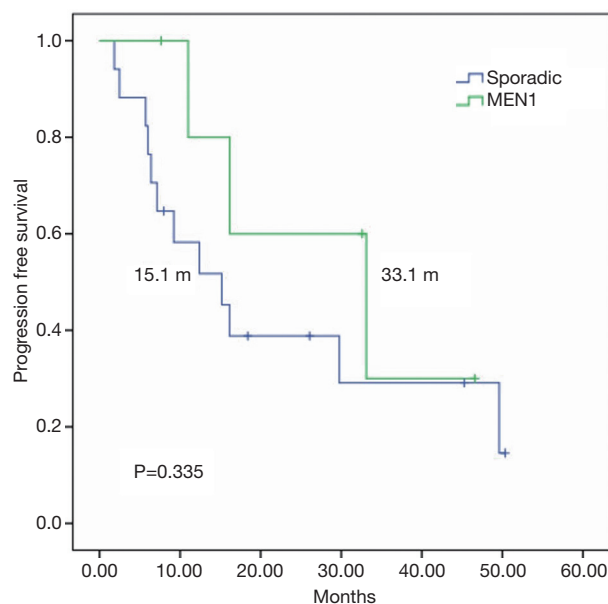


Figure 4 Median progression free survival after treatment with Everolimus in relation to the presence or absence of MEN1 in patients with pancreatic NETs grade 1–2. MEN1, multiple endocrine neoplasia type 1; NETs, neuroendocrine tumors; m, months.

survival rate of these patients is 30% to 40%, with median survival up to 44 months (17–20). One of the few case reports in the literature described a patient with pNET and genetically confirmed MEN1 syndrome who achieved 3 years of disease control with everolimus (21). Our cohort showed a numerically, albeit not statistically significant, superior mPFS and mTTF in the germline mutated group treated with everolimus, achieving a mPFS of 33 months, which seems longer than the mPFS of 12 months reported in the phase III placebo-controlled trials of everolimus (22). Compared with placebo, everolimus use was associated with a significant increase in the median PFS (11.0 *vs.* 4.6 months, $P < 0.0001$) and sub-analyses in the same cohort of patients confirmed their efficacy in all subgroups considered (prior chemotherapy, previous therapy with somatostatin analogues, performance status, age, sex, origin, well differentiated *vs.* intermediate grade tumors) (22). While the encouraging results of the mutated patients could be associated with selection bias from our small sample, the mPFS of the sporadic pNET group was quite similar—15 months—to that described in Radiant-3 trial.

Everolimus acts as a mammalian target of rapamycin (mTOR) inhibitor. The mTOR is a key protein implicated

in the pathogenesis of many types of cancer, including NETs (23). The mTOR pathway regulates growth, proliferation, metabolism, angiogenesis and apoptosis, among other critical cell functions in response to multiple signals (24). The germinal inactivation of the *MEN1* gene, when biallelic, leads to the formation of several types of NETs (14,25). Menin, the product of the *MEN1* gene, suppresses proliferation through the mTOR pathway, inhibiting the activity of serine-threonine kinase AKT1 (15). Thus, inactivating mutations in *MEN1* gene result in activation of AKT1 and, therefore, growth and proliferation. Everolimus is a standard and effective treatment in gastroenteropancreatic NETs (26) and could be particularly effective in MEN1 associated pNETs as seen in our study.

In the case of the VHL syndrome, the germline mutation of *VHL*, a tumor suppressor gene located in chromosome 3 (3p25–26) (27), leads to the development of pNETs by mechanisms not completely understood. It is known that the mutant VHL protein results in a lack of degradation of hypoxia-inducible factors (HIF) and ultimately in an uncontrolled production of factors that promote angiogenesis and tumor growth (13). In normal

tissue, HIF-1 α undergoes ubiquitination by the VHL protein, leading to the degradation of HIF-1 α (28). Under hypoxia conditions (or VHL syndrome), HIF-1 α is not degraded and accumulates in the nucleus, leading to an increased transcription of numerous hypoxia response genes [such as VEGF and carbonic anhydrase IX (Ca-IX)] (29,30). In addition, the mTOR pathway is also involved in the regulation of HIF-1 α activity (31), this explains why human cancers with aberrant mTOR signaling are prone to angiogenesis and suggests that inhibition of mTOR with everolimus might be a suitable therapeutic strategy in patients with VHL syndrome.

Considering these characteristics, another well-established treatment for pNET is the multi-tyrosine kinase inhibitor (TKI) sunitinib, because of its anti-angiogenic mechanism of action. The phase III placebo-controlled trial of sunitinib in pNETs showed that the mPFS in the treatment group was more than doubled that of the control group, demonstrating the efficacy of this therapeutic approach (32,33). This is also true for pazopanib—a similar TKI, in patients with VHL syndrome (34). Although only one patient with VHL syndrome used sunitinib in our study, the time of disease control was superior to those reported in the literature.

The retrospective nature of this study is a limitation, as well as the reduced size of the population, and the use of convenience sampling when selecting the germline mutated patients. However, given the rarity of the genetic syndromes-associated pNETs, our study brings new data on outcomes of targeted therapy, particularly everolimus, to molecularly defined NETs.

In conclusion, our study suggests that everolimus offers a prolonged tumor control in patients with MEN1 or VHL-associated pNETs. Because of the small number of patients treated with sunitinib, we cannot conclude whether its efficacy is more pronounced among VHL patients. This study sheds light on an unexplored topic and supports the hypothesis that targeted directed treatment is the future for therapy of germline- (and even sporadic) mutated pNETs.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was conducted in accordance with the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization (ICH GCP) and applicable local laws and regulatory requirements, and was approved by the Comitê de Ética em Pesquisa em Seres Humanos (CEP) of the Fundação Antonio Prudente - AC Camargo Cancer Center (2632/18).

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