

Sequential treatment in disseminated well- and intermediate-differentiated pancreatic neuroendocrine tumors: Common sense or low rationale?

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Abstract

Fortunately, the landscape of the systemic treatment for grade 1 and 2 pancreatic neuroendocrine tumors has changed in the last decade with at least four different alternatives approved in the field. Chemotherapy,

somatostatin analogues, sunitinib and everolimus remind valid options according to the most referenced international guidelines. However, and although this is something done in the routine practice, there is a lack of evidence for the use of any of these strategies after failure to the others. Moreover, further sequential alternatives in third or fourth line have never been tested prospectively. The need for a better understanding of the rationale to sequence different systemic options is even greater in non-pancreatic neuroendocrine tumors since available therapies are scarce. Sequential strategies in other solid tumors have led to a clear improvement in overall survival. This is also believed to occur in neuroendocrine tumors but no clear data on it has been delivered yet. We postulate that the different mode of action of the systemic options available for the treatment of neuroendocrine tumors may avoid the complete resistance of one option after the other and that sequential use of these agents will be translated into a longer overall survival of patients. Prospective and randomized trials that seek for the activity of drugs after failure to another systemic alternatives are highly needed in this field of neuroendocrine tumors.

Key words: Carcinoids; Everolimus; Neuroendocrine tumors; Pancreas; Overcoming resistance; Sequential-treatment; Sunitinib

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Core tip: There is a need to improve the rationale we use when approaching to a sequential systemic treatment strategy in disseminated neuroendocrine tumors. Up to now, we do not have level 1 evidence to use any systemic alternative after failure to a prior one. Widely heterogeneous populations have been recruited in larger phase III pivotal trials in neuroendocrine tumors. Therefore, it is difficult to find final conclusions from the registration trials. In this article we aim to summarize the

available evidence behind the use of different alternatives after failure to standard somatostatin analogs.

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INTRODUCTION

The sequencing of different systemic options is something that is routinely done in metastatic solid tumors where other alternatives are available. Moreover, the use of successive lines of treatment have led to an improvement in the overall survival of all major tumors like breast cancer^[1], colorectal cancer^[2], non-small cell lung cancer^[3] or renal cell carcinoma^[4] among others. In addition, the enlargement of survival is accompanied by the maintenance of patient's quality of life^[5-8]. Both goals, survival and quality of life, are the two main objectives that we are looking for in our patients with disseminated solid tumors.

The systemic management of pancreatic neuroendocrine tumors (pNETs) has dramatically changed in the last few years. Everolimus and sunitinib are novel targeted agents that have been approved recently based on a significant improvement in progression free survival against placebo^[9,10]. Caplin and cols. Recently showed that somatostatin analogues, particularly lanreotide, may have also a role in tumor growth control and not only as a symptom-relievers in pNETs^[11]. Streptozocin-based schemes of chemotherapy have been widely used worldwide for the last three decades to treat metastatic pNETs on the basis of high tumor and symptom responses found in prospective and retrospective studies^[12-14]. Temozolomide is an alkylating agent that has shown impressive response rates according to objectives RECIST criteria but in non-randomized trials and retrospective series in pNETs^[15,16]. Based on the induced-rate of tumor shrinkage, temozolomide is also considered an option for the systemic treatment of pNETs in the most referenced international guidelines^[17-19] (Figure 1).

OVERCOMING RESISTANCES IN PNETS: THE BASIC SCIENCE PERSPECTIVE

The deep exomic sequences analysis of tumor samples from pNETs patients showed that there are at least two genetic key drivers that are leading the development of these tumors^[20]. The phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin (mTOR) pathway is directly or indirectly affected by mutations in patients with pNETs^[20]. Indirect mutations related with the mTOR

pathway are related with the biallelic inactivation of the *MEN1* tumor suppressor gene. The activity of the protein encoded by *MEN1* gene, the menin, is involved in the regulation of AKT access to the cell membrane. Therefore, a loss of function of the menin activity translates into a highest availability of AKT in tumor cell membrane that activates the mTOR signalling pathway^[21].

The second most frequently mutated genes in patients with pNETs are affecting to domain-associated protein gene (*DAXX*) and ATR-X gene (*ATRX*). A total of 43% of the patients are harbouring mutations in either *DAXX* or *ATRX* genes. Both genes are encoding proteins involved in chromatin remodelling process and are also related to the activation of alternative lengthening of telomeres^[22].

From the histology analysis and phenotype features perspective, these tumors are also characterized by high presence of newly tumor-formed blood vessels and somatostatin receptors on the surface of tumor cells. Overexpression of vascular endothelial growth factor receptors not only in the endothelial cells or in the stroma but also in the surface of the neuroendocrine cells has been extensively observed^[23,24]. The presence of somatostatin receptors over the surface of pNETs tumor cells is over 90%^[25,26]. Somatostatin receptors are playing a crucial role not only in the production and release of active peptides by the tumor cells but also in the growth and tumor cell survival process.

The complexity of the underlying biology behind the development of neuroendocrine tumors makes that it is difficult to believe that by targeting one of these involved mechanisms we can control the growing of the tumor for a prolonged period of time in the majority of the patients. At the same time, this complexity means that it is also very likely that one agent targeting one of these pathways could easily revert the resistance to the action of another agent against other mechanism. Overlapping resistance is not frequent among different approaches in the mode of action.

OVERCOMING RESISTANCES IN PNETS: THE CURRENT CLINICAL PERSPECTIVE

A wide range of agents with distinct mode of actions is used in the systemic treatment of pNETs. In renal cell carcinomas (RCC) it is established that mTOR inhibitors can overcome the resistance to tyrosine kinase inhibitors^[27]. Moreover, there is a clear strategy for sequencing treatments in RCC; tyrosine kinase inhibitors should go first and after progression mTOR inhibitors are leading to a higher overall survival^[28]. This clear superiority of sunitinib vs everolimus has not been established in neuroendocrine tumors so far.

In the RADIANT-3 trial, everolimus significantly prolonged median progression-free survival compared with placebo in 410 patients with pNETs (11.0 mo vs 4.6 mo; HR = 0.35; 95%CI: 0.27-0.45; $P < 0.001$)^[9]. In an

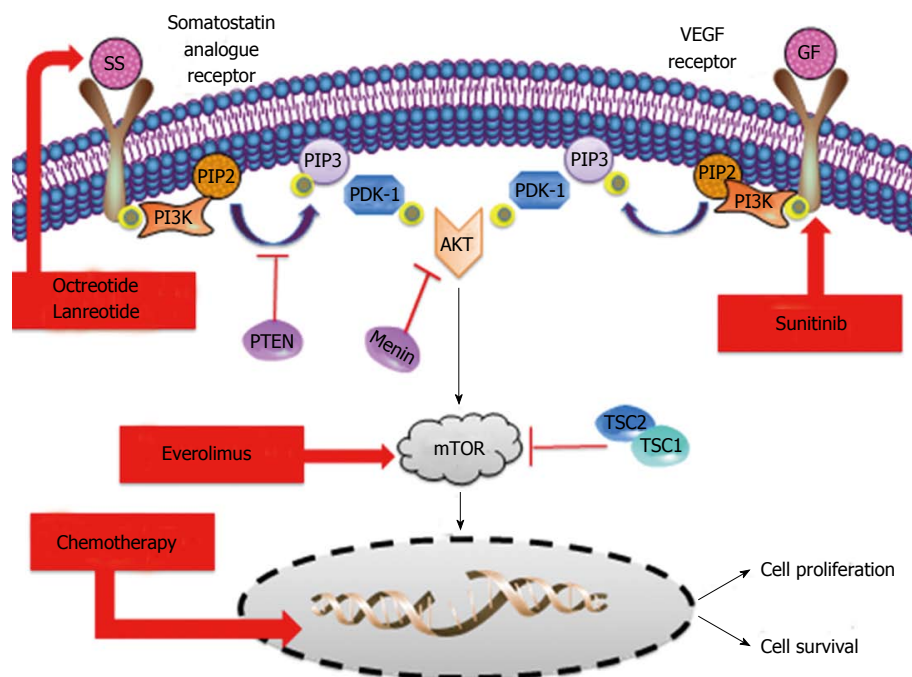


Figure 1 Summary of the mode of actions of the different available alternatives for the systemic management of pancreatic neuroendocrine tumor patients. PNET: Pancreatic neuroendocrine tumor; VEGF: Vascular endothelial growth factor; PI3K: Phosphatidylinositol 3-kinase; mTOR: Mammalian target of rapamycin.

ulterior retrospective analysis of the RADIANT-3 trial, it was shown that everolimus improved median progression free survival by 7.8 mo in patients who previously received chemotherapy (11.0 mo vs 3.2 mo; HR = 0.34; 95%CI: 0.25-0.48; $P < 0.0001$) and by 6.0 mo (11.4 mo vs 5.4 mo; HR = 0.42; 95%CI: 0.29-0.60; $P < 0.0001$) in patients who were chemo-naïve. It is important also to highlight that patients recruited for the RADIANT-3 trial were stratified according to if they received or not prior treatment with chemotherapy. Therefore, no significant differences are found in baseline characteristics of the two subgroups of patients^[29]. Same findings were found in the retrospective subgroup analysis of those patients who were recruited for the RADIANT-3 trial and received prior treatment with somatostatin analogues (0.40: 95%CI: 0.28-0.57) vs those who did not receive prior treatment with either lanreotide or octreotide (0.36: 95%CI: 0.25-0.51)^[9].

Similar findings were observed at the SUN-1111, the pivotal trial for sunitinib in advanced pNETs patients. When we take a look in deep to the forest plot analysis of the clinical outcome of patients treated at the SUN-1111 trial we observe that those patients who were treated before with somatostatin analogues had very similar HR for progression free survival (0.43: 95%CI: 0.21-0.89) than those patients recruited who were naïve for somatostatin analogues treatment (0.41: 95%CI: 0.22-0.75). In addition, there was also a highly significant benefit in terms of progression free survival in favour to those patients who did not receive or only received one systemic prior treatment and were randomized to sunitinib vs placebo (0.33: 95%CI: 0.19-0.59). Although not statistically significant there was observed also a trend to

a higher benefit for sunitinib vs placebo in those patients who received more than two prior lines of systemic treatments (0.61: 95%CI: 0.27-1.37)^[10].

To our knowledge, there are not prospective data to support the clinical activity of sunitinib followed by everolimus or the other sequence around in advanced pNETs patients. In an evidence-based sense, there is no available evidence to support the use of somatostatin analogues or chemotherapy after failure to novel targeted agents. The fact that novel targeted agents have shown activity after failure to somatostatin analogues and/or chemotherapy does not necessarily means that novel drugs should be used later in our sequential strategy of management of these patients. Actually, everolimus and sunitinib could be sequenced before the use of other systemic alternatives.

ROLE OF OTHER TARGETED AGENTS IN THE RESISTANCE OF SUNITINIB AND EVEROLIMUS

The Spanish Task Force Group for Neuroendocrine tumors (GETNE) has recently published the results of the PAZONET trial. We recruited 44 patients with advanced NETs that were treated with the multitargeted tyrosine kinase inhibitor pazopanib as a single agent ($n = 14$) or in combination with somatostatin analogues ($n = 30$) according to the investigators decision. Eleven (25%) patients had previously received everolimus, 16 (36.4%) previously received a tyrosine kinase inhibitor, and 8 patients previously had failed to both mTOR and antiangiogenic systemic treatments. The

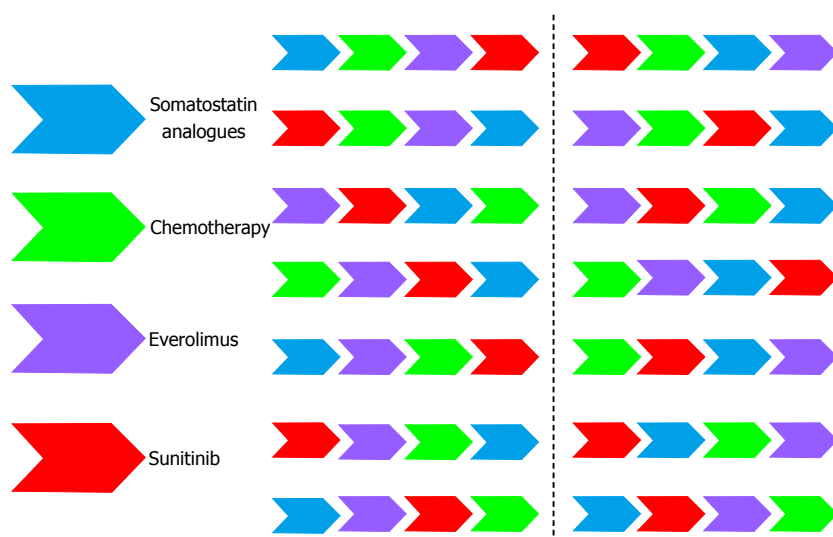


Figure 2 Different sequential alternatives to be used in advanced pancreatic neuroendocrine tumor patients based on approved agents. The term "chemotherapy" may include streptozocin ± 5-fluorouracil or doxorubicin, or temozolomide ± capecitabine.

median progression free survival that we achieved in the intention to treat population was 9.5 mo (95%CI: 4.8-14.1), however the median progression free survival in the subgroup of patients with one prior multitargeted inhibitor or a prior mTOR treatment were 12.4 mo (95%CI: 11.3-13.5) and 6.8 mo (95%CI: 0.0-15.3) respectively. The time to treatment failure was much lower in those patients who received both different alternatives before since median progression free survival was only 4.0 mo (95%CI: 1.3-6.8). Interestingly, those patients who received pazopanib plus somatostatin analogues did it better in terms of progression free survival than those who received pazopanib alone (11.7 mo, 95%CI: 9.7-13.7 vs 4.2 mo, 95%CI: 3.3-5.1; $P = 0.043$)^[30].

Bevacizumab has been widely studied either alone^[31] or in combination with octreotide^[32,33], temsirolimus^[34], everolimus^[35,36], chemotherapy^[37-39] or sorafenib^[40] in patients with disseminated NETs. Although there were some of these patients previously treated with chemotherapy or other targeted agents, no data regarding clinical outcome for these subgroup populations has been released yet.

THE CRYSTAL BALL: WHAT WOULD BE THE FUTURE OF SEQUENTIAL TREATMENT IN DISSEMINATED PNETS?

There are four different strategies currently approved or widely accepted for the treatment of advanced pNETs: Somatostatin analogues (lanreotide and octreotide), chemotherapy schemes (streptozocin- and temozolamide-based), everolimus and sunitinib. In addition, there are colleagues that are using interferon as well for pNETs patients and in those sites with availability the use of peptide receptor radionuclide therapy is also common. Therefore, we can count on at least six different systemic approaches for the routine management of

disseminated pNETs in addition of local techniques. How we can best order these alternatives is crucial to achieve the longest survival with the higher preservation of patient's quality of life.

There is a wide range of different sequential alternatives that can be followed in our patients with advanced pNETs (Figure 2). It is not reliable to conduct one trial in each of these situations. To our knowledge, the only randomized sequential trial in pNETs that is now undergoing is the European Neuroendocrine Tumors Society/Spanish Task Force Group for Neuroendocrine Tumors (GETNE) trial called SEQTOR (NCT02246127). The SEQTOR trial seeks to compare the efficacy and safety of everolimus followed by chemotherapy with streptozocin-fluorouracil (STZ-5FU) upon progression or the reverse sequence in advanced progressive pNETs.

The GETNE group is also leading the PALBONET trial that consists on a phase II trial in which the cyclin-dependent kinase-4 (CDK4)/CDK6 inhibitor palbociclib is assessed as single agents in disseminated pNETs patients after progression to at least one prior novel targeted agent.

Nowadays, and in order to be pragmatic, we should consider classical clinical parameters like if the tumor is functioning or not, presence of symptoms because of tumor bulk, rapidness of tumor growth, Ki67 proliferation index, histology grade of differentiation, comorbidities, etc., to customize our treatment. After progression to our first approach we need to consider once again all these parameters and customize the treatment one more time in a common sense based more than in evidence based sense. There is no single sequential strategy that has proved to be superior to others as of yet. Moreover, there is no single treatment that has shown to be superior to the others. This remains the challenge of neuroendocrine tumors in which "art" is still the standard of care line after line of treatment. There is an urgent need for increasing our systemic armamentarium against these tumors and

for ordering our sequential strategies. More evidence is needed across different lines of treatment for pNETs. In addition, the concomitant use of the available options could be synergistic but we do not know if the total time to tumor growth is superior to the administration of the different strategies alone one after the other. Probably, the greatest advances and efforts that are being performed in the field of molecular biology of these tumors may translate sooner than later into a better management of our patients in the clinic.

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