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EDITORIAL

Management of Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs) in 2017

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Despite new promising effective therapies that have evolved in the past few years for the well-differentiated Gastroenteropancreatic neuroendocrine tumors (GEP-NETs), advanced metastatic GEP-NETs continues to be an incurable disease with poor prognosis. The relative rarity of GEP-NETs makes it difficult to conduct large randomized trials. There is no standard guideline regarding the optimal selection and sequencing of treatment strategies for patients with advanced GEP-NETs. Surgical resection to remove the primary tumor remains the mainstay of treatment for resectable disease. More commonly, patients with GEP-NETs present with metastases at the time of diagnosis. In selected patients with isolated hepatic metastases, palliative debulking surgery and liver-directed therapies are appropriate options and may probably prolong survival [1, 2]. In patients who are not candidates for complete resection due to multiple hepatic metastases, hepatic artery embolization to reduce tumor burden is an option with tumor response rates of more than 50% in most studies [3, 4]. Somatostatin analogs are excellent options for symptom control in functional GEP-NETs [5, 6]. However, in patients with pNETs such as, insulinoma, use of somatostatin analogs may worsen hypoglycemia. Therefore, close monitoring is warranted in patients with insulinoma if somatostatin analogs are used [5, 6]. Additionally, the PROMID study and in particular, CLARINET study have demonstrated that somatostatin analogs also have antitumor activity in well-differentiated NETs [5]. Of particular note, the antiproliferative effect of lanreotide was evident not only in patients with carcinoid tumors but also in patients with pNETs. The PROMID study showed that long-acting octreotide significantly improved time to progression in treatment-naïve patients with midgut carcinoids only, and its use in controlling tumor growth in NETs of other primary sites or in non-functioning endocrine tumors of the GEP system remains undefined. In addition, it is not currently FDA approved for PFS in patients with GEP-NETs. In CLARINET study, lanreotide reduced the risk of disease progression by 53% compared with placebo for patients with metastatic GEP-NETs [6, 7]. The agent was well tolerated; however, glycemic status and the development of gallstones should be closely monitored. Of particular note, in this study, the hazard ratio favored lanreotide versus placebo regardless of hepatic burden, whereas in PROMID study, the most favorable results with octreotide were seen in patients with a low hepatic tumor load [5]. Based on the compelling evidence from CLARINET trial, SSAs are the appropriate first-line therapy for those patients with well-differentiated PNETs. Furthermore, while in the past the responses to such therapy were defined symptomatically and biochemically, now with the CLARINET study findings, we should also look for objective (i.e. radiologic) evidence [6, 7]. Studies on newer SSAs, such as pasireotide, and combination of SSAs with targeted therapies are currently underway and may help those patients who are not able to tolerate octreotide or lanreotide. It would also be interesting to study if lanreotide could benefit those patients who cannot tolerate or fail octreotide, or vice versa [8]. Also just a month ago, FDA approved a supplemental indication for lanreotide Injection 120 mg for the treatment of carcinoid syndrome; when used, it reduces the frequency of short-acting somatostatin analogue rescue therapy.

Although extra-pancreatic NETs are generally resistant to cytotoxic chemotherapies, pNETs are found to be more responsive. Streptozocin-based and temazolamide-based regimens are the most active alkylating agents-based therapies [9, 10, 11, 12]. Studies have shown comparable overall response rates but never been compared against each other. As discussed previously, studies on the combination of capecitabine and temazolamide provide promising evidence that this regimen could potentially be an option for patients with advanced neuroendocrine tumors who have progressed on standard treatment, and warrants validation in randomized studies [13, 14].

Targeted therapies such as everolimus and sunitinib resulted in statistically significant improvements in PFS in

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randomized studies, and can be used in well to moderately differentiated metastatic pNETs [15, 16]. However, they are rarely associated with objective radiographic tumor shrinkage by Response Evaluation Criteria in Solid Tumors (RECIST) and the response rates associated with these agents are quite low as well. The choice between everolimus and sunitinib is difficult as they have very similar improvements in PFS in phase III clinical trials [17]. One major criticism of the results of both phase III studies would be that significant improvement of PFS is just a surrogate marker, since significant prolongation of OS has not been shown. However, the design of a phase III study with OS as primary endpoint and a study power of 90% would require an estimated sample size of 2800 patients in order to show that a survival benefit of 4 months is significant. Keeping in mind the low incidence rate of pNETs, successful recruitment of a sufficient number of subjects into such a study would not be feasible. But the ease of oral form of administration of both drugs seems to be a great advantage in comparison with intravenous agents. Analysis of data from many of these studies on two agents have indicated that benefit can be maintained across various subgroups, including subgroups defined according to whether patients had or had not received previous antitumor treatments. Not to forget, these agents resulted in an increase incidence of drug-related toxicities by a factor of 2 (everolimus) and 3 (sunitinib), respectively, as compared with placebo; though majority of these adverse events are generally manageable either with dose reduction or temporary interruption, or combination of both strategies [17]. Additional predictive biomarkers of response to sunitinib and everolimus for pNETs patient selection are needed. Until now there had been no head-to-head comparison of these two drugs [18]. In this situation, one should tailor a therapy based on the side effects profile and the comorbidities of the patients. Given the vasogenic effects of VEGF inhibitors, patients with uncontrolled hypertension, renal insufficiency, or other vascular disorders should be cautioned about the potential adverse effects or choosing other modalities of therapy. mTOR inhibitors can also cause significant adverse reactions such as hyperglycemia and diarrhea, which have been reported repeatedly in clinical trials. Moreover, length of treatment whether continuous or intermittent and best treatment regimen for patients with tumor relapses has to be clarified such as our colleagues have determined in treating patients with renal cell carcinoma, e.g. switching to the other drug or combination of sunitinib and everolimus or adding a Somatostatin analogue [17, 18]. In the near future, pazopanib seems to have the potential to become another alternative for the treatment of patients with progressed pNETs according to current study data.

Peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin analogues relies on the expression of somatostatin receptors by neuroendocrine tumor cells, which allows delivery of a cytotoxic radiolabeled compound directly to the tumor. Two different radiolabels are most frequently used: analogues labeled with 90Yttrium (90Y), or analogues labeled with 177Lutetium (177Lu). The 90Y has greater beta energy and tissue penetration than 177Lu. 90Y may therefore have greater activity against larger tumors but also possibly higher toxicity, especially nephrotoxicity. PRRT holds immense interest, especially in North America. It seems to be a promising treatment option and finally the results of a randomized controlled Phase III NETTER-1 trial (NCT01578239) were presented involving 230 patients randomized in 36 European and 15 sites in the United States. At the time of statistical analysis, he median PFS was not reached for Lutathera and was 8.4 months with 60 mg Octreotide LAR [95% CI: 5.8-11.0 months], $p < 0.0001$, with a hazard ratio of 0.21 [95% CI: 0.13-0.34]. Within the current evaluable patient dataset for tumor responses ($n = 201$), the number of CR+PR was 19 (18.8%) in the Lutathera group and 3 (3.0%) in the Octreotide LAR 60 mg group ($p < 0.0004$). Although the OS data were not mature enough for a definitive analysis, the number of deaths was 13 in the Lutathera group and 22 in the Octreotide LAR 60 mg group ($p < 0.019$ at interim analysis) which suggests an improvement in overall survival [19].

Studies on cancer stem cells (CSCs) have led to the discovery of novel therapeutic targets in many other malignancies. Katsuta *et al*. identified CSCs in PNET clinical specimens and cell lines. Immunohistochemical analysis of clinical tissue samples demonstrated a significant correlation between CD73 expression and the invasion into adjacent organs. Since CD73 was suggested to be a potential biomarker of anti-PD-1 immune checkpoint therapy, CD73 might be a promising therapeutic target for PNET CSCs [20]. Ongoing clinical trials are testing the efficacy of immune modulating antibodies against the PD-1/PDL-1 pathway (i.e. Avelumab in Merkel Cell Carcinoma) in pre-treated, progressing neuroendocrine tumors (NCT01772004, NCT01375842).

Telotristat ethyl was recently approved by FDA for the treatment of inadequately controlled carcinoid syndrome symptoms in metastatic NET patients on SSA therapy [21]. Results from multiple phase I-III clinical studies of telotristat ethyl therapy have reported a significant decrease in the daily bowel movement frequency, increase in quality of life and the subsequent decrease in annual health costs related to carcinoid syndrome symptoms in NET patients. In addition to improvement in diarrhea, there was associated decrease in urinary 5-hydroxyindoleacetic acid (u5-HIAA) which provides the evidence that telotristat ethyl effectively decreases serotonin production. This findings set up the rationale to investigate the role of this agent to mitigate serotonin-mediated complications in this patient population, especially cardiac valvular disease or mesenteric fibrosis [22].

Biomarkers may be used to assist in both the diagnosis and post-treatment follow up in patients with pNETs. In poorly differentiated tumors, chromogranin-A (CgA), synaptophysin and cytokeratin are often used to establish neuroendocrine differentiation. Ki-67 (MB-1) and the

mitotic rate are used as grading criteria for NETs and were shown to correlate with outcome [22, 23]. Blood markers, such as pancreatic polypeptide (PPP) and specific serum hormone levels are also used to diagnose pNETs and evaluate response to therapy. Plasma levels of chromogranin-A are thought to correlate with tumor burden and increased levels have been associated with a poor PFS and survival [24]. PPP is a nonspecific biomarker for nonfunctioning pNETs with a relatively low sensitivity (63%) and specificity (81%). However, when used in combination with CgA, the sensitivity for nonfunctioning pNETs increased from 68% to 93%. For functioning pNETs, the levels of the secreted hormone represent a more specific tumor marker [25]. As per the National Comprehensive Cancer Network (NCCN) guidelines, serum proinsulin, insulin/glucose ratio and C-peptide levels may be followed in insulinomas; serum gastrin levels may be followed in gastrinomas; serum VIP levels may be followed in VIPomas; serum glucagon, glucose and CBCs may be followed in glucagonomas; serum Somatostatin, calcitonin and parathyroid hormone related peptide levels may be followed in other functioning pNETs. Novel biomarkers are currently being evaluated, including neuron-specific enolase (NSE) [23], circulating tumor cells (CTCs), and placental growth factor. Currently, no definitively proven predictive biomarkers are available to guide selection of therapies. Therefore, further studies are needed to individualize and optimize their management. Over the past few years, knowledge regarding the molecular pathology of Pancreatic NETs has increased substantially. PNETs are characterized by a relatively limited number of mutations in tumor suppressor genes, such as MEN1, ATRX and DAXX. The clinical significance and potential for treatment of these mutations remains uncertain.

To summarize, historically, GEP-NETs are a heterogeneous group of diseases with limited treatment options. However, other questions, such as the optimal timing, selection and sequence of therapies, biomarkers that predict response to the novel agents in an individual patient remain to be answered. We propose a step-wised approach for management of advanced GEP-NETs and utilizing a multidisciplinary team of expertise. With the new advances in understanding the genetic and molecular pathogenesis, GEP-NETs have become an entity for which investigators and the pharmaceutical industry alike have a newfound interest in drug development, research and clinical trials. The next decade of research is bright in GEP-NETs and should provide new insights into the molecular underpinnings of this disease, therapy selection and sequencing of the available therapies.

Conflict of Interest

The authors have no potential conflicts of interest

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