JOP. J Pancreas (Online) 2012 Jul 10; 13(4):372-375.

HIGHLIGHT ARTICLE

Update on Novel Therapies for Pancreatic Neuroendocrine Tumors

Highlights from the "2012 ASCO Annual Meeting". Chicago, IL, USA; May 31 - June 5, 2012

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Summary

Neuroendocrine tumors (NETs) describe a heterogeneous group of tumors with a wide range of morphologic, functional, and behavioral characteristics. Pancreatic neuroendocrine tumors (pNET) are a subset of NETs which are increasing in incidence and prevalence. These tumors are generally slow growing and behave in an indolent fashion. However, when these tumors spread they can be life threatening and difficult to treat with current modalities. In 2011, the landscape of treatment for pNET was changed with the approval of two targeted agents, sunitinib and everolimus, the first new therapies for this disease in over 20 years. Data from these clinical trials and extensive preclinical work into the underlying molecular pathways in neuroendocrine tumors has generated intense interest in the quest to identify additional effective agents in this challenging disease. At the 2012 American Society of Clinical Oncology (ASCO) Annual Meeting, several researchers presented updated data regarding the use of targeted agents, alternative chemotherapeutic agents and combinations of these in the treatment of pNET. Corrie *et al*. (Abstract #4121) reported data from a chemotherapy clinical trial replacing 5-FU with capecitabine and evaluating the addition of cisplatin in NETs. Several authors reviewed the addition of the anti VEGF monoclonal antibody bevacizumab into combination therapy. Ducreux *et al* (Abstract #4036) presented results from a trial of chemotherapy plus bevacizumab while Firdaus *et al*. (Abstract #4127) reported the results of combination therapy with octreotide, bevacizumab, and pertuzumab. Hobday *et al*. (Abstract #4048) reported positive results of an interim analysis of combination therapy with an mTOR inhibitor and bevacizumab. Kulke *et al* (Abstract #4125) reported the results of a clinical trial utilizing an antibody targeting the insulin growth factor receptor. Finally, Vinik *et al*. (Abstract #4118) provided updated survival data form the seminal phase III trial that led to approval of sunitinib in the treatment of pNET. The authors review and summarize these abstracts in this article.

What Did We Know Before the 2012 American Society of Clinical Oncology (ASCO) Annual Meeting?

Neuroendocrine tumors (NETs) consist of a diverse group of tumors composed of cells showing neuroendocrine cell differentiation (secretory granules), a subset of which can be further classified by their dominant secretory products. Although it was thought that the neuroendocrine cells that give rise to NETs migrated from the neural crest to the gut endoderm, it is now apparent that enteropancreatic neuroendocrine cells originate from multipotent stem cells that give rise to all epithelial cell types in the gastrointestinal tract and pancreas [1]. NETs show heterogeneity in morphologic, functional and clinical features [2]. A subset of NETs involving the pancreas previously termed islet cell tumors or islet cell carcinomas are designated pancreatic NETs (pNETs.) Although pNET represent a small percentage of all pancreatic tumors (1.3%), the prevalence of these tumors is significant (9.9% of all pancreatic tumors) and the incidence is increasing [3]. In tertiary oncology centers, the majority of patients with malignant pNETs represent advanced stage tumors with approximately 65% of patients presenting with unresectable or metastatic disease [4].

Prior to 2011, the only approved agent for unresectable disease was streptozocin which was approved prior to 1984 after demonstrating some efficacy in early trials (either alone [5] or in combination with doxorubicin [6] or 5-FU [7]). Further studies have questioned the efficacy of streptozocin [8] and there had not been any new drugs approved in the last 20 years. As a result patients with unresectable pNETs have a poor prognosis. The median survival time for patients with distant metastatic disease is 24 months [4], the 5-year survival rate of patients with metastatic disease is 30-

Key words Drug Therapy; everolimus; Neuroendocrine Tumors; Pancreatic Neoplasms; sunitinib; Vascular Endothelial Growth Factors

Abbreviations NET: neuroendocrine tumors; pNET: pancreatic neuroendocrine tumors; PS: performance status.

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40% [9] and has not changed for 20 years. The effort to find improved therapeutics for pNET was bolstered by the observation that there are several inherited cancer syndromes which are associated with pNET (including multiple endocrine neoplasia type 1 (MEN1), von Hippel-Lindau disease (vHL), neurofibromatosis 1 (NF1), and the tuberous sclerosis complex (TSC)) [10]. Unfortunately the underlying genetic abnormalities in these syndromes are relevant in only a subset of the sporadic pNETs [11]. A global gene expression analysis of pNETs revealed that at least two important genes in the mammalian target of rapamycin (mTOR) pathway (*TSC2* and *PTEN*) were downregulated in 85% of primary tumors [12, 13]. Additionally, aberrant expression of several tyrosine kinase receptors and overexpression of vascular endothelial growth factor (VEGF) have also been noted in pNET [13]. Utilizing this preclinical data, two targeted agents demonstrated prolongation of progression free survival in advanced pNET and were approved for this indication in 2011. In the RAD001 in Advanced Neuroendocrine Tumors (RADIANT)-3 trial, an inhibitor of the mammalian target of rapamycin (mTOR), everolimus was superior to placebo in prolonging progression free survival in patients with unresectable, advanced pNET from 4.6 to 11.0 months [14]. Another phase III trial looked at the multi-kinase inhibitor, sunitinib, in unresectable pNET and found an improvement in progression free survival from 5.5 to 11.4 months when compared to placebo [15]. Despite these impressive results in improving progression free survival, the response rate to these targeted therapies remains low. There are ongoing efforts to improve on this therapy by more potent targeting of these pathways, by combination therapy, and by identification of additional targets. One promising target is the insulin-like growth factor pathway since both the ligand (IGF) and the cognate receptor (IGF-1R) are frequently expressed in neuroendocrine tumors [16]. There is also at least one report that indicates that some patients with neuroendocrine tumors have upregulation of the HER-2 protein [17] and that this may be an additional target for therapy.

At the 2012 ASCO Annual Meeting, several abstracts were presented highlighting this novel research and reported the results of clinical trials to identify novel and improved therapy for the treatment of pNET. These reports are reviewed and summarized here.

What We Learned at the American Society of Clinical Oncology (ASCO) Annual Meeting

Updated Chemotherapy Regimens

Chemotherapy has been used in the treatment of NET for many years; streptozocin was approved by the FDA for this indication prior to 1984. A randomized controlled trial demonstrated that addition of 5-FU to streptozocin was associated with improved response [18] and this combination has been frequently used. In many tumors, the oral prodrug capecitabine has shown similar efficacy when used as replacement for 5-FU, often with a favorable safety profile. A case series described several responses with the combination of

Table 1. Summary of abstracts regarding treatment of pancreatic neuroendocrine tumors presented at the 2012 American Society of Clinical Oncology (ASCO) Annual Meeting.

Abstract	Trial design	Study population	Intervention	Results	Comments
Vinik, *et al*. #4118 [25]	Phase III, randomized controlled, double blinded	Unresectable, well differentiated pNET 171 patients	Sunitinib *vs*. placebo	Median overall survival: Sunitinib: 33.0 months Placebo: 26.7 months HR=0.71; P=0.11	Did not reach significance 69% of placebo patients crossed over to sunitinib
Corrie, *et al*. #4121 [20] NET01 trial	Phase II, two arms, randomized	Unresectable, advanced or metastatic NET (48% were pNET) 86 patients (41 with pNET)	Capecitabine + streptozocin (CS) *vs*. capecitabine + streptozocin + cisplatin (CSC)	Partial response: 8% *vs*. 14% Stable disease: 74% *vs*. 64% mPFS: 10.2 *vs*. 9.7 months (All for CS *vs*. CSC)	Capecitabine may be a substitute for 5-FU Response rate was lower than expected Cisplatin did not seem to add benefit
Ducreux, *et al*. #4036 [21] BETTER study	Phase II, open label, two groups [a]	Progressive, metastatic, well differentiated pNET 34 patients (1 group)	5-FU + streptozocin + bevacizumab [a]	Partial response: 56% (19/34) [a] Stable disease: 44% (15/34) [a] mPFS= 23.7 months [a]	Grade 3 or 4 toxicity was seen in 68% [a]
Hobday, *et al*. #4048 [23]	Phase II, single arm	Progressive, well or moderately differentiated pNET 25 patients (interim analysis)	Temsirolimus + bevacizumab	Partial response: 52% (13/25) 6-month PFS: 84% (21/25)	Study is ongoing Encouraging response
Kulke, *et al*. #4125 [24]	Phase II, single arm	Metastatic, low or intermediate grade NET (50% were pNET) 60 patients (30 with pNET)	AMG479 (monoclonal antibody to IGF-1R)	Partial response: 0% mPFS: 6.3 months (4.2 months in pNET)	Treatment was well tolerated but little response
Firdaus, *et al*. #4127 [22]	Phase II, single arm	Advanced well differentiated NET (26% with pNET) 43 patients (11 with pNET)	Bevacizumab + pertuzumab + octreotide LAR	Response rate: 16% (1 CR) mPFS: 8.2 months (6.4 months for pNET)	Median overall survival not yet reached

5-FU: 5-flurouracil; CS: capecitabine + streptozocin; CSC: capecitabine + streptozocin+ cisplatin; HR: hazard ratio; IGF-1R: insulin growth factor 1 receptor; LAR: long acting release; mPFS: median progression free survival; NET: neuroendocrine tumors; PFS: progression free survival; pNET: pancreatic neuroendocrine tumors

[a] There were two groups in the trial but data were only presented regarding one group (the one noted)

streptozocin, capecitabine, and cisplatin [19] and this provided the rationale for a clinical trial of this combination. In Abstract #4121 [20], Corrie *et al*. described the results of this clinical trial. They conducted a prospective, randomized phase II trial looking at the role of combination capecitabine/ streptozocin plus or minus cisplatin in advanced NETs with 48% of the patients enrolled with pNET. As summarized in Table 1 they found similar outcomes with the two treatment groups with increased toxicity in the more aggressive treatment arm (cisplatin group.) Of note, the response rate of both arms was low with partial response seen in 14% and 8% but the overall disease control rate was close to 80% with either regimen.

Addition of Bevacizumab

Several abstracts looked at the role of bevacizumab in the treatment of advanced pNET. Sunitinib is thought to work at least in part by inhibition of the VEGF pathway and VEGF is overexpressed in pNET [13] leading to significant interest in incorporating the anti-VEGF monoclonal antibody bevacizumab in the treatment of this disease.

In Abstract #4036 [21], Ducreux *et al*. reported results from one group of a phase II trial looking at the activity of bevacizumab in combination with standard chemotherapy with 5-FU/streptozocin in patients with metastatic, progressive, well differentiated pNETs. The primary outcome was progression free-survival and at this report the median progression free survival was 23.7 months. The combination therapy was associated with a very high rate of response (19 of 34; 55.9%) but grade 3 or 4 adverse events (as measured by common toxicity criteria (CTC)) were also common, occurring in 23 of 34 patients (67.6%). This combination seems to have encouraging activity and may be further investigated in appropriate patients in a phase III setting.

In Abstract #4127 [22], Firdaus *et al*. reported on an ambitious phase II trials looking at a combination of targeted agents. The investigators enrolled healthy patients with advanced, well differentiated NETs (including 26% with pNET) and treated them with octreotide (Sandostatin® LAR, Novartis Pharmaceuticals Co., East Hanover, NJ, USA), bevacizumab, and pertuzumab- a monoclonal antibody that disrupts HER-2 signaling. The combination was associated with some response (as noted in Table 1) and may lead to further investigation in a controlled trial.

In Abstract #4048 [23], Hobday *et al*. reported the results of an interim analysis of a phase II trial looking at the combination of mTOR inhibition with temsirolimus and VEGF inhibition with bevacizumab. The combination treatment is being investigated in patients with well or moderately differentiated pNET who have progressive disease. The interim analysis was performed after enrolling 25 of the planned 50 patients and it showed a high rate of response with 13 patients (52%) demonstrating a radiographic partial response. The study is continuing accrual, further safety analysis will be important to evaluate tolerability of this regimen but the high response rate is encouraging.

Other Targeted Agents

In Abstract #4125 [24], Kulke *et al*. reported on a phase II trial evaluating the use of an investigational targeted therapy directed against IGF-1R. The insulin growth factor receptor is thought to play a role in progression of neuroendocrine tumors so they evaluated the role of a monoclonal antibody against IGF-1R in patients with metastatic, progression neuroendocrine tumors. Although this agent was well tolerated, there were no radiographic responses by Response Evaluation Criteria in Solid Tumors (RECIST) criteria. It is not known if there will eventually be a biomarker that may select a subset of patients that can benefit from this therapy but at this time is was not effective in this unselected population.

Finally, in Abstract #4118 [25], Vinik *et al*. reported updated results from the large phase III trial that demonstrated superiority of sunitinib compared to placebo in prolonging time to progression. At the time of the initial analysis there were few deaths (30 out of 171 or 18%), potentially limiting the survival analysis. At the time of this updated analysis, 51% of the patients have died (87 of 171) and the median overall survival is now estimated at 33.0 months in the intervention group (sunitinib) and 26.7 months in the placebo group. This result did not reach significance with a hazard ratio of 0.71 (95% CI: 0.47-1.09; P=0.11). As previously reported most patients in the placebo arm (69%) crossed over to receive sunitinib on progression limiting the ability to detect a difference in mortality due to this intervention.

Discussion

As NETs increase in incidence the spectrum of available therapy is also increasing. There has been a suggestion that some of the increased incidence in this diagnosis is due to improvements in diagnostic imaging with detection of smaller lesions in addition to the incidental diagnosis of asymptomatic cases [26]. However, for the group of advanced or malignant NET, effective treatment options will need to be identified through well designed clinical trials. Recently two targeted agents have been approved by the FDA for the treatment of progressive pNET. Everolimus is an mTOR inhibitor which inhibits cell growth, proliferation, and angiogenesis. Sunitinib is a multi-kinase inhibitor that is thought to have an effect in pNET through inhibition of vascular endothelial growth factor (VEGF) which plays a role in angiogenesis. As summarized above, there were several abstracts presented at the 2012 ASCO Annual Meeting which represent important contributions to this field. Chemotherapy plays an important role for many patients and report by Corrie *et al*. [20] suggest

that capecitabine is a safe combination with streptozocin; however, the response rate is low and it does not seem that cisplatin adds substantially to this regimen. Ducreux *et al*. [21] have demonstrated that chemotherapy and targeted therapy can be combined in the treatment of pNET with impressive efficacy, though the need to minimize toxicity is noted. Inhibition of IGF-1R does not seem to lead to response in pNET but there were promising preliminary results suggesting that combination of mTOR inhibition and VEGF blockade may add substantial benefit.

In summary, the abstracts presented at the 2012 ASCO Annual Meeting highlight the continued progress in developing novel treatments to improve outcomes in advanced pancreatic neuroendocrine tumors. The continued identification of new agents that are being tested in clinical trials suggests that there is promise in the future treatment for patients suffering from this form of pancreatic malignancy.

Conflict of interest The authors have no potential conflicts of interest

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