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HIGHLIGHT ARTICLE

Update on Novel Therapies for Pancreatic Neuroendocrine Tumors: 2013

Highlights from the "2013 ASCO Annual Meeting". Chicago, IL, USA; May 30 - June 4, 2013

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Summary

Neuroendocrine tumors of the pancreas (pNETs) are classified on the basis of their differentiation as well as the functional status. Current treatment options for non resectable disease include everolimus, sunitinib, somatostatin analogs and chemotherapy. A number of trials with novel compounds and drug combinations were reported at the recent ASCO Annual Meeting. Pasireotide is a novel somatostatin analog with broader affinity for the somatostatin receptors compared to the traditional octreotide and lantreotide and it appears to be safe in patients with pNETs according to a phase I study (Abstract #e15126). The combination of octreotide with everolimus showed promising response rate and progression free survival in a phase II study (Abstract #4136). In another phase II study, the AKT inhibitor MK-2206 was well tolerated with moderate efficacy (Abstract #e15133). Last but not least, we discuss the updated data from a phase II study that used the combination of temsirolimus with bevacizumab in patients with advanced pNETs (Abstract #4032).

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

Tumors with neuroendocrine differentiation comprise of a diverse set of malignant neoplasms that share common pathogenic, morphologic and clinical features. Neuroendocrine neoplastic cells are believed to originate from pluripotent stem cells, they contain secretory granules and they often present with syndromes that are linked to secreted hormones [1]. Pancreatic neuroendocrine tumors (pNETs), formerly known as islet cell tumors, account for 1% of the newly diagnosed pancreatic cancers and are further classified as functional or non-functional on the basis of hormone secretion [2]. Most of the tumors in the former group are insulinomas which are usually benign, followed by glucagonomas, gastrinomas, somatostatinomas, VIPomas, polypeptidomas and cholecystokininomas. Based on histology they are divided in three categories, well differentiated/low grade, well differentiated/intermediate grade and poorly differentiated/high grade. Most of pNETs are sporadic, but they can be associated with germline missense and nonsense mutations in the context of multiple endocrine neoplasia type 1 (MEN1) syndrome [3].

Treatment is largely dependent on the functional status and the stage. For resectable disease, surgery is generally recommended. In the case of locoregional unresectable and metastatic disease, recent trials indicate that sunitinib [4], everolimus [5] and somatostatin analogs [6] offer a progression free survival benefit. Preclinical data support the effect of these drugs on the natural history of pNETs: the vascular endothelial growth factor (VEGF) pathway which is targeted by sunitinib, the mammalian target of rapamycin (mTOR) which is inhibited by everolimus and the somatostatin receptors are often aberrantly expressed in pNETs [7, 8, 9]. In addition to the biologically targeted therapies, conventional chemotherapy with combinations of 5-FU, doxorubicin and streptozocin, capecitabine and oxaliplatin or temozolomide have been reported to cause objective responses in 23% to 70% of the patients with pNETs in phase II studies [10, 11].

Key words bevacizumab; MK 2206; Neuroendocrine Tumors; pasireotide; temsirolimus

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In this review we summarize the data about the novel agents in pNETs presented in the recent 2013 ASCO Annual Meeting.

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

MK-2206 in Metastatic Neuroendocrine Tumors (Abstract #e15133 [12])

The AKT inhibitor MK-2206 was used in a phase II study for the treatment of metastatic well differentiated neuroendocrine tumors that had progressed on other treatments [12]. The investigators recruited eight patients two of whom had pNETs. In addition they studied archived tissue from the tumors for biomarker analysis. Overall, one durable response in a patient with thymic carcinoid was noted whereas three patients experienced transient stabilization of their disease. The most common side effects were hyperglycemia, transaminitis and rash. Translational analysis with next generation sequencing in the patient who responded to treatment did not reveal any relevant biomarker with the potential to serve as a companion diagnostic.

Somatostatin Analogs (Abstracts #e15126 [13] and #4136 [14])

Pasireotide is a novel somatostatin analog that binds more broadly to somatostatin receptors (SSTR1-3 and 5) compared to the traditional octreotide and lanreotide (SSTR2). Phan *et al*. [13] reported preliminary results from a phase I study of pasireotide in advanced neuroendocrine tumors. In this report, 3 patients with pNETs were recruited out of a total of 15 patients. The rest of the patients in the study suffer from either small intestinal or lung neuroendocrine tumors. Most of the patients had been treated already with other somatostatin analogs. The study was designed to escalate the dose of the study drug beginning from 80 mg up to 220 mg. At the time the preliminary results were reported, there were 6 patients who were treated with 80 mg and 9 patients treated with 120 mg. No dose limiting toxicity was noted. Most common side effects were included hyperglycemia (87%) including 2 patients with grade 3 hyperglycemia, diarrhea (53%), abdominal pain (47%), nausea (40%), anemia (33%), and fatigue (33%).

Although both everolimus and somatostatin analogs have been approved for the treatment of pNETs, the combination of the two has not been well studied. Patients with well differentiated metastatic neuroendocrine tumors who were treatment naïve, received everolimus and octreotide in the approved doses in a phase II trial performed by the Italian Trials in Medical Oncology group [14]. One third of the patients had pNETs while the rest of the neuroendocrine tumors had a small bowel, lung or unknown primary. The study enrolled 50 patients and objective response rate was the primary endpoint in the study: two patients achieved a complete response and an additional eight patients had a partial response. Disease control rate, as defined by the patients who experienced either a complete or partial response or had stable disease, was 92%. Patients progressed after a median of 16.2 months. Major side effects included one patient with grade 4 mucositis, one patient with grade 3 rash, four patients with grade 3 stomatitis and eleven patients with grade 3 diarrhea.

Combination of mTOR and VEGF Pathways in pNETs (Abstract #4032 [15])

Hobday *et al*. reported the updated data on a phase II study where patients with well or moderately differentiated pNETs were treated with the combination of temsirolimus and bevacizumab [15]. A total of 55 patients who had progressed on previous treatments were enrolled in the study. Primary endpoints were the objective response rate and progression free survival. In the 55 patients who were evaluated for the former endpoint, the response rate by using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria was 37%. About half of the 49 patients (49%) who were evaluated for progression free survival, were progression free at 12 months. Grade 3-4 side events included hypertension, hyperglycemia, fatigue, leukopenia, headache, proteinuria, and hypokalemia.

A summary of the reviewed studies is presented in Table 1.

Discussion

There have been a number of abstracts in the recent 2013 ASCO Annual Meeting that considered novel agents in the treatment of pancreatic neuroendocrine tumors. The frequent overexpression of the PI3K/AKT/mTOR pathway in pNETs provides rationale for the use of AKT inhibition. In addition, the approved drug everolimus abrogates mTORC2 but not mTORC1. Reidy *et al*. reported the effect of the AKT inhibitor MK-2206 in patients with metastatic neuroendocrine tumors [12]. Although MK-2206 was found to be well tolerated in this study, conclusion about the efficacy of the drug is limited given the small number of patients and the even smaller number of the study subjects who had a pancreatic variant.

The phase I study by Phan *et al*. [13] is consistent with results from earlier studies [16] about the safety of the novel somatostatin analog pasireotide that has a broader affinity for somatostatin receptors compared to octreotide or

Table 1. Summary of the studies on novel agents on pancreatic neuroendocrine tumors (pNETs) from the 2013 ASCO Annual Meeting.

Author (Abstract)	Design	Population (No. of cases)	Study drug	Efficiency	Grade 3-4 side effects
Reidy *et al*. (#e15133) [12]	Phase II	Metastatic NETs (n=8; 2 had pNETs)	MK-2206	4 patients had stable disease; no partial response or complete response	Hyperglycemia (37.5%) Transaminitis (37.5%) Rash (37.5%)
Phan *et al*. (#e15126) [13]	Phase I	Patients with advanced, well or moderately differentiated NETs (n=15; 3 had pNETs)	Pasireotide LAR	87% of the patients had stable disease	Hyperglycemia (13.3%)
Bajetta *et al*. (#4136) [14]	Phase II	Patients with advanced, well differentiated previously untreated neuroendocrine tumors of the GEP tract (n=50; 14 had pNETs)	Everolimus plus octreotide LAR	4% of the patients had complete response; 16% had partial response and 72% had stable disease. Median time to progression was 16.3 months	Mucositis (2%) Rash (2%) Stomatitis (8%) Diarrhea (22%)
Hobday *et al*. (#4032) [15]	Phase II	Patients with well or moderately differentiated pNETs that had progressed on previous treatments (n=55)	Temsirolimus plus bevacizumab	37% of the patients had partial response, 49% were progression free at 12 months	Hypertension (18%) Hyperglycemia (13%) Fatigue (11%) Leukopenia (9%) Headache (9%) Proteinuria (7%) Hypokalemia (7%)

GEP: gastroenteropancreatic; LAR: long acting repeatable; NETs: neuroendocrine tumors

lanreotide. Interestingly, the drug was well tolerated even at the dose of 120 mg while there was a correlation between the dose and the serum levels. Bajetta *et al*. reported the results from a phase II study with the combination of everolimus and long acting repeatable (LAR) octreotide [14]. Data on progression free survival look promising when compared to the historical data on everolimus and are consistent with the progression free survival that was achieved with this combination in a phase III trial in patients with neuroendocrine tumors and carcinoid syndrome [17]. However, more research on this combination is required.

Conclusions

In conclusion, in the 2013 ASCO Annual Meeting we saw the updated results from the phase II study of the temsirolimus plus bevacizumab combination in pNETs [15]. Results are consistent with the preliminary interim analysis that was presented in the 2012 ASCO Annual Meeting [18]; the combination of mTOR plus VEGF inhibition arises as a promising strategy in patients with advanced non resectable pNETs. Further studies are needed to show whether the combination is superior to sequential monotherapy.

Conflict of interest The authors have no potential conflict of interest

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