JOP. J Pancreas (Online) 2010 Mar 5; 11(2):135-138.

HIGHLIGHT ARTICLE

Neuroendocrine Tumors of the Pancreas: What's New

Highlights from the "2010 ASCO Gastrointestinal Cancers Symposium". Orlando, FL, USA. January 22-24, 2010

Anastasios T Dimou[1], Konstantinos N Syrigos[2], Muhammad Wasif Saif [2]

[1]Yale Pathology Department and [2]Yale Cancer Center, Yale University School of Medicine. New Haven, CT, USA

Summary

Surgical excision has been the mainstay of treatment for neuroendocrine tumors of the pancreas (PNET). Compounds like streptozocin and dacarbazin have been traditionally used in inoperable cases and somatostatin to treat syndromes deriving from functional tumors. However, a lot of progress has taken place in the area of molecular characterization of these tumors, revealing activation of mammalian target of rapamycin (mTOR) and VEGF pathways. Recent data from the 2010 ASCO Gastrointestinal Cancers Symposium demonstrate antitumor activity of everolimus, an mTOR inhibitor in combination with temozolomide in a phase I/II trial and of sunitinib *versus* placebo in a randomized double blinded phase III trial. The role of modern biologic compounds in the treatment of PNET is not clear yet. In addition, combination of resection and transarterial chemoembolization (TACE) has been proven effective over either modality alone in the treatment of PNET metastatic to the liver in a retrospective analysis. This comes to address the problem of selecting local intervention in a metastatic disease, which has been a reasonable choice for this group of tumors in the past. Last but not least the role of Ki-67 in decision-making in PNET is being discussed.

Introduction

Pancreatic neuroendocrine tumors (PNET) are a rare subgroup of tumors found in the pancreas and can be either functional or non-functional [1, 2, 3]. Their appearance in histology sections has little to contribute to their malignant potential since this traditionally depends on the extent of their spread. However, recent WHO classification classifies PNET into well differentiated tumors, well differentiated carcinomas and poorly differentiated carcinomas in an attempt to predict natural history from the pathology report [1]. They are usually sporadic but they may also appear among other features of genetic syndromes like multiple endocrine neoplasia type I or von Hippel-Lindau disease. Patients usually present with syndromes induced by hormones secreted from functional tumors, or with mass effects from non-functional tumors. Functional PNET can secrete biologically active peptides like insulin, gastrin, glucagon, somatostatin, vasoactive intestinal polypeptide (VIP), whereas non-functional tumors also express and secrete peptides like neurotensin or chromogranin A, which are not active [1].

Most of the PNET are already metastatic by the time they are diagnosed and liver is the most common site of metastasis. Regional lymph node spread is also common. PNET are non-functional in their majority and the absence of a distinct functional syndrome as well as their indolent course and subsequent delay in diagnosis is mainly responsible for the advanced stage at the time of diagnosis [2, 3]. PNET have a 5-year survival that can range from 97% in benign insulinomas to as low as 30% in non-functional metastatic PNET [2, 3]. In addition, more recent data demonstrate that poorly differentiated PNET can have similar prognosis with adenocarcinomas of the gastrointestinal tract [2].

Surgery with curative intent is the mainstay of treatment for localized or loco-regional disease [1, 2]. Surgery as well as other forms of local treatment like transarterial chemoembolization or radiofrequency ablation can also improve prognosis in patients with liver metastases [2, 4, 5]. For the inoperable cases, cytotoxic therapy with compounds like streptozotocin, 5-fluorouracil or doxorubicin can achieve modest outcome [6, 7, 8, 9]. Treatment with somatostatin

Key words Chemoembolization, Therapeutic; everolimus; Ki-67 Antigen; mTOR protein; Neuroendocrine Tumors; sunitinib

Abbreviations mTOR: mammalian target of rapamycin; NET: neuroendocrine tumor; PTEN: phosphatase and tensin homolog; TSCII: tuberous sclerosis complex II

Correspondence Muhammad Wasif Saif
Yale Cancer Center, Yale University School of Medicine, 333 Cedar Street, FMP 116, New Haven, CT,USA
Phone: +1-203.737.1569; Fax: +1-203.785.3788
E-mail: wasif.saif@yale.edu

Document URL http://www.joplink.net/prev/201003/12.html

Table 1. Abstracts from 2010 ASCO Gastrointestinal Cancers Symposium concerning pancreatic neuroendocrine tumors.

Abstract	Description	Comments
#127 Raymond E, *et al*. [10]	Sunitinib vs placebo in metastatic PNET	Phase III
#223 Kulke M, *et al*. [11]	Everolimus plus temozolomide in patients with advanced PNET	Phase I/II
#234 Celinsky SA, *et al*. [12]	Resection *vs*. transarterial chemoemblization in metastatic PNET to the liver	Retrospective analysis
#266 Singh S, *et al*. [13]	Ki-67 in the evaluation of neuroendocrine tumors	Retrospective chart review

PNET: pancreatic neuroendocrine tumors

analogues like octreotide has been proven to prolong progression-free survival in patients with metastatic neuroendocrine tumors of midgut origin [9].

This is a review of the recent advances in PNET as they were reported in four abstracts presented at the 2010 ASCO Gastrointestinal Cancers Symposium (Table 1).

A Randomized Double Blinded Trial of Sunitinib *versus* Placebo in Patients with Advanced PNET

Abstract #127: Updated results of the phase III trial of sunitinib (SU) versus placebo (PBO) for treatment of advanced pancreatic neuroendocrine tumors (NET) [10]

Sunitinib, which is a multi-tyrosine kinase inhibitor, was compared in this randomized, double-blinded phase III study to placebo as salvage treatment in patients with well differentiated tumors of the pancreas after documented progression. The trial, initially intended to recruit 340 patients, but was ended after 171 patients enrolled (86 in the sunitinib group and 85 in the placebo group) due to profound benefit in the sunitinib arm. Primary endpoint was the progression-free survival. Patients who received sunitinib had a median progression-free survival of 11.4 months *versus* 5.5 months for the patients who received placebo (P=0.0001; HR=0.418, 95% CI: 0.263-0.662). Objective response rate was 9.3% in the sunitinib arm and 0% in the placebo arm (P=0.0066). Sunitinib caused 3/4 neutropenia in 12% of the patients *versus* 0% in the placebo arm, grade 3/4 hypertension in 9.6% *versus* 1.2% and palmar-plantar erythrodysesthesia in 6.0% *versus* 0 %. However, the population was not representative of the general population of PNET, because it included only well differentiated tumors and the proportion of non-functional tumors was 50%, which is less than what it has been historically considered to be [2, 3]. Furthermore, it would be interesting to test the control rate that sunitinib can achieve for the syndromes that accompany the functional tumors.

Safety and Efficiency Profile of Everolimus plus Temozolomide in Patients with Advanced PNET: A Phase I/II Study

Abstract #223: Phase I/II study of everolimus (RAD001) in combination with temozolomide (TMZ) in patients (pts) with advanced pancreatic neuroendocrine tumors (NET) [11]

Everolimus is a compound that inhibits the mammalian target of rapamycin (mTOR) and temozolomide is an oral alkylating agent, while both of them have been suggested as treatment options in the metastatic setting of neuroendocrine tumors. This group performed a phase I/II trial that tests the tolerability and efficacy of the combination of those two agents in patients with advanced PNET. Two dose levels of everolimus, 5 and 10 mg *per os qd* were combined with the fixed dose 150 mg/m^2 *per os qd* of temozolomide for seven consecutive days every other week. After six four-week cycles temozolomide was stopped and the patient would keep on with everolimus only. At the first dose level except for 1 out of 6 evaluable patients no other dose-limiting toxicity (DLT) was reported (Table 2). The group of patients that received treatment at the second dose level was also used as the phase II population and consisted of 17 patients with performance status (PS) 0 or 1 that received a median of 6 cycles. Sixteen of those were evaluable for toxicity and grade 3/4 hematologic toxicity was reported in 11 patients, whereas grade 3/4 non-hematologic toxicity was reported in 4 patients (Table 2). All 17 patients were evaluable for efficacy. Overall control rate of the disease was 88% (Table 2). Forty-five percent of the patients experienced a decrease in their chromogranin A levels of more than 50%. No data is provided concerning any previous treatments the patients received, the metastatic sites and the tumor burden as well as the grade and other histology aspects of the tumors that would bear a possible association with treatment efficacy.

Table 2. Safety data of everolimous and temozolomide in pancreatic neuroendocrine tumors.

Everolimus dose level	No. of cases	Safety-phase I (grade 3/4 reactions)		Efficacy-phase II
		Hematologic	Non-hematologic	
5 mg/m^2	6	Thrombocytopenia: 1 (16.7%)	None	None
10 mg/m^2	17	Thrombocytopenia: 4 (23.5%) Lymphopenia: 5 (29.4%) Neutropenia: 2 (11.8%)	Triglyceride elevation: 1 (5.9%) Transaminases elevation: 1 (5.9%) Hyperglycemia: 1 (5.9%) Rash: 1 (5.9%)	Objective response rate: 6 (35%) Disease stabilization rate: 9 (53%) Progression rate: 2 (12%)

Transarterial Chemoembolization (TACE) *versus* Resection of Liver Metastases from a NET Primary

Abstract #234: Multimodality management of neuroendocrine tumors metastatic to the liver [12]

TACE was compared to resection and to the combination of the two in a retrospective analysis of 124 patients with neuroendocrine tumors (NET) that had metastasized to the liver. The different treatment groups were balanced in terms of gender, age, site of primary tumor and presence of symptoms. Treatment with the combination of resection and TACE was the more efficacious followed by resection alone and TACE alone (mean survivals: 148 months *versus* 131 months *versus* 42 months, respectively; P=0.001). Patients who had their liver metastases resected were more likely to have their primary tumor resected as well than patients who underwent TACE (83% *versus* 17%). Younger age was associated with better outcome. Multivariate analysis including age, resection of the primary tumor and treatment type, showed that age and treatment type were independent predictors of overall survival (P=0.009 and P=0.010, respectively). It is not clear from the abstract the number of patients that were included in each group. In addition, data concerning the performance status of the patients and the differentiation of the tumors and whether those characteristics were balanced between the groups would be useful as they could influence the prognosis of the patients. This analysis refers to neuroendocrine tumors in general without specification for pancreatic origin. In addition patients with better performance status are expected to have undergone resection rather than TACE, which would introduce some bias in the analysis. Last but not least, the conclusion is drawn on the basis of the mean overall survivals in each group whereas the median would be more appropriate as the distribution of overall survival is not known (Table 3).

Table 3. Efficacy data from transarterial chemoembolization and/or resection in liver metastases from pancreatic neuroendocrine tumors.

Treatment modality	Mean survival
Transarterial chemoembolization (TACE)	42 months
Resection	131 months
Transarterial chemoembolization (TACE) + resection	148 months
	P=0.001

Ki-67: How Often Is It Used in the Workup of Patients with NET?

Abstract #266: The role of Ki-67 in the prognosis and management of neuroendocrine (NET) patients in a multidisciplinary cancer center [13]

In this retrospective analysis from a multi-disciplinary cancer center, 82 patients with neuroendocrine tumors were studied for Ki-67 expression. Ki-67 was categorized into four levels and patients were assigned to four groups according to the level of Ki-67 expression. Patients with metastatic disease were found to have higher levels of Ki-67 and patients that received chemotherapy and/or hormonal therapy were more likely to have higher Ki-67 levels. However, symptom control was found to be similar in all the Ki-67 groups. The investigators do not mention the origin of the neuroendocrine tumors. In addition, the conclusion that Ki-67 levels influence treatment decisions for those tumors is not fully supported by the data, as it is indicated that there is an association rather than an influence. Furthermore, no statistical considerations are taken into account to demonstrate this association.

Discussion

Neuroendocrine tumors are a rare subset of pancreatic tumors, but their incidence is rising during the last two decades [2]. They are traditionally considered to have indolent course. However, the majority of them is metastatic at the time of diagnosis and if poorly differentiated, their prognosis can be dismal. Surgery has been suggested for the resectable cases. For those that cannot be resected, old chemotherapy regimens have been used in the past. Data concerning the newer biologic compounds is lacking. In addition, it is not clear, whether TACE can be comparable to resection of liver metastases.

Activation of the mTOR pathway has been found to be common in the neuroendocrine tumors of the pancreas through the inactivation and loss of the mTOR inhibitors tuberous sclerosis complex II (TSCII) and phosphatase and tensin homolog (PTEN) [14]. Briefly, mTOR is integrating signals coming from receptors in the cell membrane and is implicated in cell proliferation and anti-apoptotic pathways via pS6k and 4EBP1 which are the main molecules downstream of mTOR. Akt is the major activator whereas TSCII and PTEN are the major inhibitors of mTOR. Downregulation of TSCII and PTEN were significantly associated with worse differentiation, worse prognosis and liver metastases in patients with PNET [14]. Furthermore, mTOR inhibitors like everolimus (RAD001) and everolimus have demonstrated antiproliferative effects in pancreatic neuroendocrine cell lines [15, 16, 17]. Everolimus, alone or in combination with octreotide have been moderatively effective in pancreatic neuroendocrine tumors in a phase II trial [18, 19]. Temozolomide and decarbonizes have been proposed in the past as chemotherapy options in the metastatic setting of PNET [8, 20]. Kulke *et al*. [11] are the first to test the safety of the combination of temozolomide with everolimus in patients with advanced PNET and to provide some insight into the possible antitumor effect of the combination of traditional chemotherapy with the newer biologic agents in those tumors. More phase II trials will clarify whether a phase III trial of this combination is feasible.

Vascular endothelial growth factor (VEGF) has been implicated in the pathogenesis of neuroendocrine tumors [21, 22] and makes anti-angiogenesis therapy a reasonable choice for clinical trials. Sunitinib is a

multi-target tyrosine kinase inhibitor that has demonstrated anti-tumor activity in phase II clinical trials in PNET with an acceptable toxicity profile [23]. Raymond *et al*. [10] presented the first phase III trial of sunitinib in patients with advanced PNET. Their study demonstrated clear clinical benefit of sunitinib over placebo and had to close early because the primary endpoint was shown after 171 patients were randomized. However, results should be interpreted with caution, as the population did not include poorly differentiated tumors.

TACE has been a minimally invasive procedure that has been proposed for the treatment of liver metastases instead of resection and it has been debatable whether it can substitute surgery. Celinsky *et al*. [12] showed that resection should be preferred when possible and even combined with TACE for better outcomes. Overall, PNET can be of dismal prognosis for a large proportion of patients with this disease. Recent advances reported in the 2010 ASCO Gastrointestinal Cancers Symposium were based on advances concerning the molecular characterization of those tumors and underscore the priority of understanding their biologic behavior that will provide rationale for the clinical trials to come.

Disclosure of interest None

References

1. Ehehalt F, Saeger HD, Schmidt CM, Grützmann R. Neuroendocrine tumors of the pancreas. Oncologist 2009;14:456-67. [PMID 19411317]

2. Franko J, Feng W, Yip L, Genovese E, Moser AJ. Non-functional neuroendocrine carcinoma of the P pancreas: incidence, tumor biology, and outcomes in 2,158 patients. J Gastrointest Surg 2010; 14:541-8. [PMID 19997980]

3. Halfdanarson TR, Rabe KG, Rubin J, Petersen GM. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. Ann Oncol 2008; 19:1727-33. [PMID 18515795]

4. Liu DM, Kennedy A, Turner D, Rose SC, Kee ST, Whiting S, et al. Minimally invasive techniques in management of hepatic neuroendocrine metastatic disease. Am J Clin Oncol 2009; 32:200-15. [PMID 19346815]

5. Hill JS, McPhee JT, McDade TP, Zhou Z, Sullivan ME, Whalen GF, Tseng JF. Pancreatic neuroendocrine tumors: the impact of surgical resection on survival. Cancer 2009; 115:741-51. [PMID 19130464]

6. Moertel CG, Lefkopoulo M, Lipsitz S, Hahn RG, Klaassen D. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. N Engl J Med 1992; 326:519-23. [PMID 1310159]

7. Kouvaraki MA, Ajani JA, Hoff P, Wolff R, Evans DB, Lozano R, Yao JC. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. J Clin Oncol 2004; 22:4762-71. [PMID 15570077]

8. Ramanathan RK, Cnaan A, Hahn RG, Carbone PP, Haller DG. Phase II trial of dacarbazine (DTIC) in advanced pancreatic islet cell carcinoma. Study of the Eastern Cooperative Oncology Group-E6282. Ann Oncol 2001; 12:1139-43. [PMID 11583197]

9. Arnold R, Müller H, Schade-Brittinger C, Rinke A, Klose K, Barth P, et al. Placebo-controlled, double-blind, prospective, randomized study of the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: A report from the PROMID study group. ASCO Annual Meeting 2009:Abstracts 4508.

10. Raymond E, Niccoli-Sire P, Bang Y, Borbath I, Lombard-Bohas C,Valle JW, et al. Updated results of the phase III trial of sunitinib (SU) versus placebo (PBO) for treatment of advanced pancreatic neuroendocrine tumors (NET). 2010 ASCO Gastrointestinal Cancers Symposium. Abstract No. 127.

11. Kulke M, Blaszkowsky LS, Zhu AX, Florio S, Regan E, Ryan DP, Chan JA. Phase I/II study of everolimus (RAD001) in combination with temozolomide (TMZ) in patients (pts) with advanced pancreatic neuroendocrine tumors (NET). 2010 ASCO Gastrointestinal Cancers Symposium. Abstract No. 223.

12. Celinski SA, Nguyen KT, Steel JL, Mehra R, Marsh JW, Geller DA, et al. Multimodality management of neuroendocrine tumors metastatic to the liver. 2010 ASCO Gastrointestinal Cancers Symposium. Abstract No. 234.

13. Singh S, Rowsell C, IngbeN, Law C. The role of Ki-67 in the prognosis and management of neuroendocrine (NET) patients in a multidisciplinary cancer center. 2010 ASCO Gastrointestinal Cancers Symposium. Abstract No. 266.

14. Missiaglia E, Dalai I, Barbi S, Beghelli S, Falconi M, della Peruta M, et al. Pancreatic endocrine tumors: expression profiling evidences a role for AKT-mTOR pathway. J Clin Oncol 2010; 28:245-55. [PMID 19917848]

15. Grozinsky-Glasberg S, Franchi G, Teng M, Leontiou CA, Ribeiro de Oliveira A Jr, Dalino P, et al. Octreotide and the mTOR inhibitor RAD001 (everolimus) block proliferation and interact with the Akt-mTOR-p70S6K pathway in a neuro-endocrine tumour cell Line. Neuroendocrinology 2008; 87:168-81. [PMID 18025810]

16. Zitzmann K, De Toni EN, Brand S, Göke B, Meinecke J, Spöttl G, Meyer HH, Auernhammer CJ. The novel mTOR inhibitor RAD001 (everolimus) induces antiproliferative effects in human pancreatic neuroendocrine tumor cells. Neuroendocrinology 2007; 85:54-60. [PMID 17310129]

17. Moreno A, Akcakanat A, Munsell MF, Soni A, Yao JC, Meric-Bernstam F. Antitumor activity of rapamycin and octreotide as single agents or in combination in neuroendocrine tumors. Endocr Relat Cancer 2008; 15:257-66. [PMID 18310292]

18. Yao JC, Phan AT, Chang DZ, Wolff RA, Hess K, Gupta S, et al. Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a phase II study. J Clin Oncol 2008; 26:4311-8. [PMID 18779618]

19. Yao JC, Lombard-Bohas C, Baudin E, Kvols LK, Rougier P, Ruszniewski P, et al. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. J Clin Oncol 2010; 28:69-76. [PMID 19933912]

20. Kulke MH, Stuart K, Enzinger PC, Ryan DP, Clark JEW, Muzikansky A, et al. Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors. J Clin Oncol 2006; 24:401-6. [PMID 16421420]

21. La Rosa S, Uccella S, Finzi G, Albarello L, Sessa F, Capella C. Localization of vascular endothelial growth factor and its receptors in digestive endocrine tumors: correlation with microvessel density and clinicopathologic features. Hum Pathol 2003; 34:18-27. [PMID 12605362]

22. Terris B, Scoazec JY, Rubbia L, Bregeaud L, Pepper MS, Ruszniewski P, et al. Expression of vascular endothelial growth factor in digestive neuroendocrine tumours. Histopathology 1998; 32:133-8. [PMID 9543669]

23. Kulke MH, Lenz HJ, Meropol NJ, Posey J, Ryan DP, Picus J, et al. Activity of sunitinib in patients with advanced neuroendocrine tumors. J Clin Oncol 2008; 26:3403-10. [PMID 18612155]