JOP. J Pancreas (Online) 2013 July 10; 14(4):367-371.

HIGHLIGHT ARTICLE

Neuroendocrine Tumors: Treatment Updates

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

Simon Khagi, Muhammad Wasif Saif

Tufts Medical Center, Tufts University School of Medicine. Boston, MA, USA

Summary

Neuroendocrine tumors of the gastroenteropancreatic tract remain a difficult array of neoplasia to treat. Treatment of advanced and metastatic gastroenteropancreatic neuroendocrine tumors has traditionally been difficult with few systemic treatment options. In 2011, two new targeted therapies, everolimus and sunitinib were approved for treatment of pancreatic neuroendocrine tumor. The approval of these agents led to an enhanced interest in exploring novel agents. This can be evidenced by the fact that this is the first year that ASCO assembled related abstracts under a separate title of neuroendocrine tumor. The annual American Society of Clinical Oncology (ASCO) conference in 2013 presented four abstracts (#4030, #4031, #4032, #4136) that shed light on new therapeutic options that help target the unique pathways involved in these neuroendocrine malignancies.

What Did We Know Before the 2013 American Society of Clinical Oncology (ASCO) Annual Meeting?

Neuroendocrine tumors (NETs) of the gastroenteropancreatic tract are a rare and heterogeneous form of cancer that span variable tissue subtypes with behavior patterns that reflect their invasive potential. The biological behavior of these cancers is reflected in the pathological grade ascribed to these lesions at the time of biopsy. Grading schema for these lesions help characterize a less aggressive subtype (i.e., carcinoid of the gut) from more aggressive subtypes that behave with great similarity to small cell lung carcinomas. The use of mitotic rate and Ki-67 forms the basis for assigning grade, with lesions having high levels of mitoses and Ki-67 reflecting a more aggressive pattern of biological behavior. Well differentiated NETs may have a protracted progression and cause very little symptoms, behaving as indolent neoplasms even in the metastatic setting. Poorly differentiated lesions can present with a variety of symptoms and the potential for wide metastatic spread and organ compromise (Figures 1 and 2).

Treatment modalities are based on overall staging assessment and relative patient symptoms. As mentioned above, staging involves pathologic evaluation and various imaging modalities, that both characterize the quantitative and qualitative behavior of the lesion.

Resection remains a viable option for any NET subtype which has not metastasized. However, a significant number of intermediate to poorly differentiated lesions have a high rate of recurrence. Unresectable disease remains difficult to treat, especially in the setting of advanced histological subtypes.

Known therapeutic modalities that exist involve the use of somatostatin analogs, systemic anti-neoplastic agents, and organ-specific modalities (mostly involving liver lesions). The focus of this review will be a discussion of current understanding of systemic therapy and delve into the 2013 ASCO Annual Meeting experience.

Interferon

The use of interferon therapy for NETs had been established decades ago with Oberg *et al*. showing that interferon alpha stimulates T cell to counteract NET-secreted vasoactive substances [1]. A direct cytotoxic effect had also been noted. Tumor stabilization has been noted at 40 to 50 percent.

Key words bevacizumab; Carcinoid Tumor; everolimus; Neuroendocrine Tumors; Octreotide; pasireotide; Somatostatin; temsirolimus

Abbreviations NET: neuroendocrine tumor; RADIANT: RAD001 in Advanced Neuroendocrine Tumors

Correspondence Simon Khagi
Division of Hematology and Medical Oncology; Tufts Medical Center; 800 Washington Street Box #245; Boston, MA 02111; USA
Phone: +1-617.636.5459; Fax: +1-617.636.8938
E-mail: skhagi@tuftsmedicalcenter.org

However, only 15 percent of patients have had notable regression of tumor, with significant variability in duration of response [2]. The overall use of interferon alpha as an active agent against NET has been hindered by its adverse side effect profile and the lack of large prospective trials evaluating its efficacy.

Somatostatin Analogs

Somatostatin analogs have long been shown to be efficacious in the management of gastroenteropancreatic NETs. Almost two decades ago, Rubin *et al*. reported that somatostatin analogs can be used in the treatment of NET [3]. Octreotide has been the prototypical somatostatin analog used primarily in the USA. Its mechanism of action involves competitive inhibition of somatostatin receptors, with a decrease in the secretion of vasoactive substances from NETs. The use of long acting injectable octreotide has made the management of most symptomatic NETs more tolerable in the out-patient setting, with the short acting formulation used for breakthrough symptoms. The PROMID trial in 2009 helped establish the use of octreotide as a primary hormonally targeted agent against NET in the setting of advanced small bowel carcinoid. The study showed a significant advantage of octreotide over placebo in time to progression (14.3 months *versus* 6 months) [4].

Cytotoxic Chemotherapy

Various single and combinatory cytotoxic chemotherapeutic agents have been used in the treatment of NET. Mechanisms of action stemmed from alkylation, platinum, and incorporation of pyrimidine analogs to interrupt DNA synthesis. Streptozocin has been an established agent in the treatment of locally advanced and metastatic NET. Its use has been validated by Moertel *et al*. showing a median survival of 26.4 months. A combination of streptozocin, 5-flurouracil (5-FU) and doxorubicin showed a median survival of 37 months [5]. Another alkylating agent, dacarbazine, has shown efficacy, with some studies reporting a 33 percent response rate. The use of platinum-based regimens (with the variable incorporation of 5-FU and bevacizumab) has been evaluated in small phase II trials, showing success in a subset of pancreatic NET patients [6]. However, all of the above agents carry significant toxicity profiles, which have made their use difficult in the locally advanced or metastatic setting, and in those patients with low performance statuses.

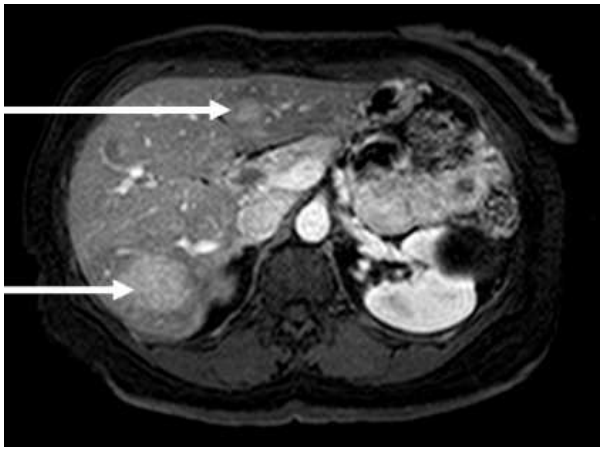

Figure 1. MRI of a patient with pancreatic neuroendocrine tumor spread to the liver (arrows).

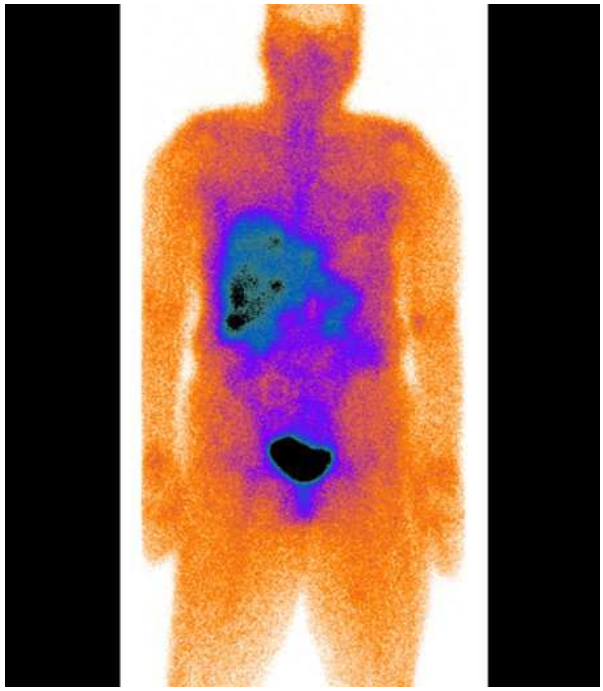

Figure 2. Nuclear octreotide scintigraphy of patient in Figure 1 (represented in false color thallium scan imaging for representative detail).

Temozolomide has also been evaluated in the setting of NET, particularly pancreatic NETs. Efficacy had been prospectively validated by Kulke *et al*. Reported response rates ranged from 24 to 45 percent [7]. A retrospective analysis revealed a potential benefit with the addition of capecitabine (CAPTEM). Response rates were reported at 70 percent [8].

Targeted Agents

Molecularly targeted agents have been looked at for several years in the setting of pancreatic NET and gastrointestinal carcinoid. Among the most promising molecular targets are tyrosine kinases, mammalian target of rapamycin (mTOR), and vascular endothelial growth factor receptors (VEGFR). Variable activity has been demonstrated, with pancreatic NET being more responsive than gastrointestinal carcinoid [9].

Sunitinib, sorafenib, and pazopanib are tyrosine kinase inhibitors that have been evaluated in pancreatic NET and gastrointestinal carcinoid. Among the three, sunitinib remains the only agent approved within the USA for use for pancreatic NET based on a small phase II trial noting partial response in 11 percent of patients and disease stability in 68 percent [10]. Tyrosine kinase inhibition has not been shown to be as robust in gastrointestinal carcinoid.

Everolimus and temsirolimus have been well studied agents that act to inhibit mTOR. The RAD001 in Advanced Neuroendocrine Tumors (RADIANT)-3 trial helped establish the use of everolimus as monotherapy in the setting of pancreatic NET [11]. It showed a significant progression free survival of 11 *versus* 4.6 months compared placebo. In the setting of advanced gastrointestinal carcinoid, the RADIANT-2 trial showed a potential benefit of everolimus added to octreotide montherapy [12]. The use of temsirolimus combined with bevacizumab has also been evaluated and showed promising results in a phase II trial that was initially presented at the 2012 ASCO GI Symposium [13] (discussion to follow).

Vascular endothelial growth factor receptor inhibition with bevacizumab has been explored in gastrointestinal carcinoid. The combination of bevacizumab and octreotide had been validated in a phase II trial by Yao *et al*. The study showed superior progression free survival when compared to the combination of octreotide and interferon [14].

What Did We Learn at the 2013 American Society of Clinical Oncology (ASCO) Annual Meeting?

The American Society of Clinical Oncology conference in 2013 featured several updates on new and existing therapeutic options for gastroenteropancreatic NET. Updated survival data were presented from the long awaited PROMID study group. A new somatostatin analog was introduced and compared directly with long acting octreotide. Additionally, updates on the use of everolimus and temsirolimus were presented.

Update on PROMID (Abstract #4030 [15])

As noted within the PROMID study performed in 2009, there was a marked clinical benefit in time to progression when assessing octreotide *versus* placebo in the setting of metastatic midgut neuroendocrine tumors. In the time period between July 2001 and January 2008, forty-two patients were randomized to octreotide and 43 patients were assigned to a placebo. Long term survival data both in the setting of high (<10%) and low (>10%) hepatic metastatic burden was collected through January 2013. The octreotide group demonstrated an extended overall survival in the setting of low hepatic metastatic burdens.

Comparison of Pasireotide and Octreotide (Abstract #4031 [16])

A randomized, blinded phase III trial comparing depot-injections of pasireotide and octreotide in the setting of poorly controlled symptoms associated with NET was presented this year. Symptom response was the primary end point, with progression free survival being a secondary endpoint. Interestingly, at six months, symptom response rates did not differ between the two groups (P=0.53); however, patients within the pasireotide group showed an improved (11.8 months) progression free survival compared to the octreotide (6.8 months) group (P=0.045).

Everolimus Plus Depot Octreotide (Abstract #4136 [17])

An Italian phase II trial looking at the efficacy of everolimus in combination with depot octreotide found an overall durable clinical benefit when taking together all patients who had a response to therapy. The study looked at 50 enrolled patients with advanced gastroenteropancreatic and lung NET. Reportedly, 92 percent derived a clinical benefit, with the majority of these patients (72%) maintaining stable disease for more than 6 months.

Temsirolimus Plus Bevacizumab (Abstract #4032 [18])

Building on the known synergistic effects of mTOR and VEGFR inhibition in the setting of pancreatic NET demonstrated in previous studies, a phase II trial combining temsirolimus and bevacizumab was designed to assess overall response rates and progression free survival. Notably, of the 55 patients enrolled on study, 44 patients were free of progressive disease at six months (80%). Response rates were notable at 37%.

Discussion

The treatment of neuroendocrine tumors of the gastroenteropancreatic system has broadened tremendously over the past several decades. We have advanced from best supportive options to multiple cytotoxic agents to the use of molecularly targeted drugs that focus on the unique biochemical pathways inherent in neuroendocrine tumors.

Recent advances in the field have focused on the expanded role of somatostatin analogs. As noted above, the PROMID trial has shown an increase in overall survival in patients with gastrointestinal NET with low hepatic metastatic burden. Given the

above data, the use of somatostatin analogs may be considered in the first line setting for advanced NET sometime in the near future.

Pasireotide, another somatostatin analog was presented at this year's ASCO Annual Meeting, and was found to have an exceptionally positive effect on progression free survival compared to octreotide. The study by Wolin *et al*. found that progression free survival was almost double compared to octreotide. However, the study was small. This speaks to the need to continue to investigate the potential role of pasireotide as a potentially beneficial agent in the upfront setting in the treatment of NET, furthering the role of somatostatin analogs.

This year's ASCO Annual Meeting also presented us with encouraging results regarding the use of mTOR inhibitors. New data on everolimus and temsirolimus were presented. A small phase II study from Italy showed promising results in the treatment of a wide variety of NET using everolimus. And Hobday *et al*. found a beneficial synergistic effect when combining temsirolimus with bevacizumab. These studies speak to the intrinsic dysregulation of the mTOR pathway in these tumors. The combination of VEGFR inhibition with mTOR inhibition presenting us with promising possibilities in treating our patients with gastroenteropancreatic NET. This opens the door to using mTOR inhibitors with other molecularly targeted agents.

Conflicts of interest The authors have no potential conflicts of interest

References

1. Oberg K, Funa K, Alm G. Effects of leukocyte interferon on clinical symptoms and hormone levels in patients with mid-gut carcinoid tumors and carcinoid syndrome. N Engl J Med. 1983;309(3):129. PMID 6191217

2. Granberg D, Eriksson B, Wilander E, Grimfjärd P, Fjällskog ML, Oberg K, Skogseid B. Experience in treatment of metastatic pulmonary carcinoid tumors. Ann Oncol. 2001;12(10):1383. PMID 11762808

3. Rubin J, Ajani J, Schirmer W, Venook AP, Bukowski R, Pommier R, Saltz L, Dandona P, Anthony L. Octreotide acetate long-acting formulation versus open-label subcutaneous octreotide acetate in malignant carcinoid syndrome. J Clin Oncol. 1999;17(2):600. PMID 10080605

4. Rinke A, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, Mayer C, Aminossadati B, Pape UF, Bläker M, Harder J, Arnold C, Gress T, Arnold R, PROMID Study Group. Placebo-controlled, double-blind, prospective, randomized study on 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. J Clin Oncol. 2009;27(28):4656. PMID 19704057

5. 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(8):519. PMID 1310159

6. 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(8):1139. PMID 11583197

7. Kulke MH, Stuart K, Enzinger PC, Ryan DP, Clark JW, Muzikansky A, Vincitore M, Michelini A, Fuchs CS. Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine. J Clin Oncol. 2006;24(3):401. PMID 16421420

8. Strosberg JR, Fine RL, Choi J, Nasir A, Coppola D, Chen DT, Helm J, Kvols L. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. Cancer. 2011;117(2):268. PMID 20824724

9. Missiaglia E, Dalai I, Barbi S, Beghelli S, Falconi M, della Peruta M, Piemonti L, Capurso G, Di Florio A, delle Fave G, Pederzoli P, Croce CM, Scarpa A. Pancreatic endocrine tumors: expression profiling evidences a role for AKT-mTOR pathway. J Clin Oncol. 2010;28(2):245. PMID 19917848

10. Kulke MH, Lenz HJ, Meropol NJ, Posey J, Ryan DP, Picus J, Bergsland E, Stuart K, Tye L, Huang X, Li JZ, Baum CM, Fuchs CS. Activity of sunitinib in patients with advanced neuroendocrine tumors. J Clin Oncol. 2008;26(20):3403. PMID 18612155

11. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, Hobday TJ, Okusaka T, Capdevila J, de Vries EG, Tomassetti P, Pavel ME, Hoosen S, Haas T, Lincy J, Lebwohl D,Öberg K, RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011;364(6):514. PMID 21306238

12. Pavel ME, Hainsworth JD, Baudin E, Peeters M, Hörsch D, Winkler RE, Klimovsky J, Lebwohl D, Jehl V, Wolin EM, Oberg K, Van Cutsem E, Yao JC, RADIANT-2 Study Group. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. Lancet. 2011;378(9808):2005. PMID 22119496

13. Hobday TJ, Qin R, Reidy DL, et al. Multicenter phase II trial of temsirolimus and bevacizumab in pancreatic neuroendocrine tumor (abstract). J Clin Oncol 2012; 30 (suppl 4): Abstract 260.

14. Yao JC, Phan A, Hoff PM, Chen HX, Charnsangavej C, Yeung SC, Hess K, Ng C, Abbruzzese JL, Ajani JA. Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b. J Clin Oncol. 2008;26(8):1316. PMID 18323556

15. R. Arnold, M. Wittenberg, A. Rinke, C. Schade-Brittinger, B. Aminossadati, E. Ronicke, T. M. Gress, H. H. Mueller, PROMID Study Group. Placebo controlled, double blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors (PROMID): Results on long-term survival. ASCO 2013 Abstract No: #4030

16. E. M. Wolin, B. Jarzab, B. Eriksson, T. Walter, C. Toumpanakis, M. Morse, P. Tomassetti, M. Weber, D. R. Fogelman, J. Ramage, D. Poon, J. M. Huang, M. Hudson, X. Zhi, J. L. Pasieka, A. Mahamat, F. Swahn, J. Newell-Price, W. Mansoor, K. E. Oberg. A multicenter, randomized, blinded, phase III study of pasireotide LAR versus octreotide LAR in patients with metastatic neuroendocrine tumors (NET) with disease-related symptoms inadequately controlled by somatostatin analogs. ASCO 2013 Abstract No:#4031

17. E. Bajetta, L. Catena, N. Fazio, S. Pusceddu, P. Biondani, G. Blanco, S. Ricci, M. Aieta, F. Pucci, M. Valente, N. Bianco, F. Bellomo, C. Mauri, P. Buonandi, V. Roberto Everolimus in combination with octreotide LAR as the first-line treatment for advanced neuroendocrine tumors: A phase II trial of the I.T.M.O. (Italian Trials in Medical Oncology*)* group. ASCO 2013 Abstract No: #4136

18. T. J. Hobday, R. Qin, M. J. Moore, D. L. Reidy, J. R. Strosberg, H. L. Kindler, M. H. Shah, H. Lenz, A. Kaubisch, H. X. Chen, C. Erlichman. Multicenter phase II trial of temsirolimus (TEM) and bevacizumab (BEV) in pancreatic neuroendocrine tumor (PNET). ASCO 2013 Abstract No: #4032