

HIGHLIGHT ARTICLE

Pancreatic Neuroendocrine Tumors: Does Chemotherapy Work?

Highlights from the "2014 ASCO Gastrointestinal Cancers Symposium".

San Francisco, CA, USA. January 16-18, 2014

Mohamedtaki Abdulaziz Tejani¹, Muhammad Wasif Saif²

¹Division of Hematology and Oncology, University of Rochester. Rochester, NY, USA. ²Section of GI Cancers and Experimental Therapeutics, Tufts University School of Medicine. Boston, MA, USA

Summary

Pancreatic neuroendocrine tumors (pNETs) are rare well-differentiated neoplasms which can be functional or non-functional. They tend to have a worse prognosis than their counterpart carcinoid tumors. Current systemic treatment options for advanced, unresectable disease include somatostatin analogs, everolimus and sunitinib. Low response rates and toxicity profiles have, thus far, limited the widespread use of cytotoxic chemotherapy in this setting. In this update, we review three abstracts from the 2014 ASCO Gastrointestinal Cancers Symposium that present outcomes of the use of combination capecitabine and temozolomide in patients with advanced pNET. We summarize their results and discuss the role of this regimen in treatment algorithms for metastatic pNET.

Introduction

Well-differentiated tumors of neuroendocrine origin within the digestive system usually arise in the gastrointestinal tract (predominantly small bowel) or pancreas. Pancreatic neuroendocrine tumors (pNETs), formerly known as islet cell tumors, are rare and make up about 1% of newly diagnosed pancreatic cancers. pNETs tend to have a worse prognosis than carcinoid tumors [1] and have a higher response rates with most antineoplastic agents. pNETs can be non-functional or functional (insulinoma, glucagonoma and gastrinoma being among the most common).

Treatment approach is dependent on stage and symptom status. For resectable tumors, surgery will generally provide prolonged survival. Metastasectomy, when feasible, can also provide prolonged control of symptoms and disease-free survival for patients with well-differentiated tumors. For patients with symptomatic disease, treatment with a somatostatin analog is

recommended which also offers a progression-free survival benefit [2]. Recent trials have demonstrated benefit in outcomes with the use of sunitinib [3] and everolimus [4] among patients with pNETs.

The benefit of conventional cytotoxic chemotherapy is less clear. Small studies have shown modest response rates with agents such as fluoropyrimidines, doxorubicin and streptozocin and these are generally reserved for patients for whom there are no other treatment options. In this article, we review data presented at the 2014 ASCO Gastrointestinal Cancers Symposium about use of chemotherapy in pNETs.

What We Have Learned at the 2014 ASCO Gastrointestinal Cancers Symposium

Prospective Phase II Study of Capecitabine and Temozolomide (CAPTEM) for Progressive Moderately and Well-Differentiated Metastatic Neuroendocrine Tumors (Abstract #179 [5]).

In this oral presentation, Fine *et al.* presented results from an interim analysis of their ongoing phase II trial utilizing capecitabine and temozolomide among 28 patients with metastatic well-moderately differentiated neuroendocrine tumors. Doses used were capecitabine 1,500 mg/m²/day divided *bid* (maximum 2,500 mg/day) on days 1-14 and temozolomide 150-200 mg/m² divided *bid* on Days 10-14, with two weeks off in a

Key words capecitabine; Neuroendocrine Tumors; temozolomide

Abbreviations CAPTEM: capecitabine and temozolomide

Correspondence Mohamedtaki Abdulaziz Tejani
Division of Hematology and Oncology; University of Rochester
Medical Center; 610 Elmwood Avenue, Box 704; Rochester, NY
14642; USA
Phone: +1-585.275.9484; Fax: +1-585.276.0350
E-mail: mohamed_tejani@urmc.rochester.edu

Table 1. Outcomes with capecitabine and temozolomide (CAPTEM) regimen in pancreatic neuroendocrine tumors (pNETs).

Study	Regimen	Number of pNET cases	Partial response rate	Stable disease	Progression free survival (months)	Overall survival (months)
Fine <i>et al.</i> [5] <i>(Abstract #179)</i>	Capecitabine 1,500 mg/m ² /day <i>bid</i> Days 1-14 Temozolomide 150-200 mg/m ² Days 10-14 of 28-day cycle	11	4 (36%)	6 (55%)	18.2	NR
Spada <i>et al.</i> [6] <i>(Abstract #281)</i>	Capecitabine 1,500 mg/m ² /day <i>bid</i> Days 1-14 Temozolomide 150-200 mg/m ² days 10-14 of 28-day cycle	14 (Overall: 29) ^a	4 (14%) ^a	17 (59%) ^a	NR	NR
Peixoto <i>et al.</i> [7] <i>(Abstract #343)</i>	Capecitabine 2,000 mg/m ² /day <i>bid</i> Days 1-14 Temozolomide 200 mg/m ² Days 10-14 of 28-day cycle	14	NR	NR	4.9	18.8
Saif <i>et al.</i> [8]	Capecitabine 1,000 mg <i>bid</i> Days 1-14 Temozolomide 200 mg/m ² Days 10-14 of 28-day cycle	7	3 (43%)	2 (29%)	8.0	NR

NR: not reported

^a Response rates in the overall study population (including carcinoid patients: n=29)

28-day cycle. Eleven patients with pNET were included in their study: 4 patients (36%) had partial responses, an additional 6 patients (55%) had stable disease and one had progressive disease (9%). Ongoing progression free survival for these patients was excellent (longer than 18.2 months). Most common grade 3 and 4 toxicities were lymphopenia, thrombocytopenia and diarrhea. The authors concluded that CAPTEM is an effective, well-tolerated regimen for patients with progressive neuroendocrine tumors.

Capecitabine plus Temozolomide in Patients with Advanced Neuroendocrine Neoplasms: An Italian Multicenter Retrospective Analysis (Abstract #281 [6]).

Spada *et al.* presented a retrospective study looking at the use of CAPTEM among their patients with well-differentiated neuroendocrine tumors. Clinical data from 29 patients were reviewed of whom 14 had pNET. Doses used were capecitabine 1,500 mg/m²/day divided *bid* on Days 1-14 and temozolomide 150-200 mg/m²/day on Days 10-14 of each 28-day cycle. The overall response rate was 14% and stable disease rate was 59%. Most common grade 3 toxicity was thrombocytopenia. Of note, all patients with partial response had *MGMT* gene inactivation and *TS*-polymorphism which the authors conclude could serve as a predictive biomarker.

Outcome of Patients Treated with Capecitabine and Temozolomide for Advanced Pancreatic Neuroendocrine Tumors (pNETs) and non-pNETs (Abstract #343 [7]).

Another retrospective study came from Peixoto *et al.* who described characteristics and outcomes

among patients treated with CAPTEM for well-differentiated neuroendocrine tumors at 6 provincial cancer treatment centers in Canada. Twenty-nine patients were included and 14 had tumors originating in the pancreas. Doses were capecitabine 2,000 mg/m²/day divided *bid* on Days 1-14 and temozolomide 200 mg/m² on Days 10-14 of each 28-day cycle. Response rates were not provided in this abstract. Progression free survival and overall survival for patients with pNET was 4.9 months and 18.8 months, respectively. The authors concluded that CAPTEM shows good activity among patients with well-differentiated neuroendocrine tumors.

Discussion

All the three abstracts reviewed here present outcomes of similarly dosed CAPTEM regimen for pancreatic neuroendocrine tumors. Limitations of these studies are relatively small numbers, retrospective nature (Abstracts #281 and #343) and non-randomized study design (Abstract #179). Also, despite a similar patient population, response rates reported by Fine *et al.* are much higher than those reported in other studies and reasons for this are unclear. Results observed in these abstracts are in line with our group's previously reported experience with CAPTEM among 7 patients with pNET [8] (Table 1). We used a similar dosing regimen with 3 patients achieving partial response and 2 patients with stable disease. More definitive data about activity of this regimen will emerge from the ongoing cooperative group trial "Temozolomide With or Without Capecitabine in Treating Patients With Advanced Pancreatic Neuroendocrine Tumors" [9]. In the interim, it is our opinion that these studies demonstrate that CAPTEM

combination is a reasonable choice for fit patients with advanced, progressive disease who have exhausted all other standard and protocol treatment options.

Conflicts of interest The authors have no potential conflicts of interest

References

1. Panzuto F, Nasoni S, Falconi M, *et al.* Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization. *Endocr Relat Cancer* 2005; 12: 1083.
 2. Rinke A, Muller HH, Schade-Brittinger C, *et al.* Placeb-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: 4656.
 3. Raymond E, Dahan L, Raoul JL, *et al.* Sunitinib maleate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011; 364: 501.
 4. Yao JC, Shah MH, Ito T, *et al.* Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011; 364: 514.
 5. Fine RL, Gulati AP, Tsushima D, *et al.* Prospective Phase II study of capecitabine and temozolamide for progressive, moderately and well-differentiated metastatic neuroendocrine tumors. *J Clin Oncol* 2014; 32: abstract 179
 6. Spada F, Fumagalli C, Antonuzzo L, *et al.* Capecitabine and temozolamide in patients with advanced neuroendocrine neoplasms: An Italian multicenter retrospective analysis. *J Clin Oncol* 2014; 32: abstract 281.
 7. Peixoto RD, Noonan K, Kennecke HF, *et al.* Outcomes of patients treated with capecitabine and temozolamide for advanced pancreatic neuroendocrine tumors (pNETs) and non-pNETs. *J Clin Oncol* 2014; 32: abstract 343.
 8. Saif MW, Kaley K, Brennan M, Garcon MC, Rodriguez G, Rodriguez T. A retrospective study of capecitabine/temozolamide (CAPTEM) regimen in the treatment of metastatic pancreatic neuroendocrine tumors after failing previous therapy. *JOP. J Pancreas (Online)* 2013; 14:498-501.
 9. U.S. National Institutes of Health. Temozolomide with or without capecitabine in treating patients with advanced pancreatic neuroendocrine tumors. *ClinicalTrials.gov* (NCT 01824875). Accessed January 28, 2014 <http://www.clinicaltrials.gov/ct2/show/NCT01824875?term=01824875&rank=1>
-