Phase I study of pasireotide (SOM 230) and everolimus (RAD001) in advanced neuroendocrine tumors

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Abstract

Octreotide and everolimus have demonstrated efficacy in neuroendocrine tumors. Pasireotide is a somatostatin analog with binding affinity to a broader range of somatostatin receptor subtypes than octreotide. We performed a phase I study to evaluate the safety and feasibility of combining pasireotide with everolimus in patients with advanced neuroendocrine tumors. Cohorts of patients with advanced neuroendocrine tumors were treated with escalating doses of pasireotide (600–1200 µg s.c. b.i.d., followed by pasireotide LAR 40–60 mg i.m. monthly) and everolimus (5–10 mg daily). Twenty-one patients were treated. Dose-limiting toxicities consisting of grade 3 rash and grade 3 diarrhea were observed. Twelve patients were safely treated at the maximum protocol-defined dose level of pasireotide LAR 60 mg i.m. monthly and everolimus 10 mg daily. Hyperglycemia was common; other observed toxicities were consistent with the known toxicities of either agent alone. Partial tumor response was observed in one patient; 17 (81%) patients experienced at least some tumor regression as their best response to therapy. In conclusion, pasireotide LAR 60 mg i.m. monthly in combination with everolimus 10 mg daily is feasible and associated with preliminary evidence of antitumor activity in patients with advanced neuroendocrine tumors. Further studies evaluating this combination are warranted.

Endocrine-Related Cancer (2012) 19 615–623

Introduction

Somatostatin analogs have been widely used in patients with advanced neuroendocrine tumors for the treatment of carcinoid syndrome and related symptoms of hormone hypersecretion (Kvols *et al.* 1986, di Bartolomeo *et al.* 1996, Oberg *et al.* 2004). More recently, treatment with the somatostatin analog octreotide has also shown to slow tumor progression in patients with advanced carcinoid tumors. In the PROMID study, patients receiving octreotide had a significantly longer median time to tumor progression than those randomized to receive placebo (14.3 vs 6 months) (Rinke *et al.* 2009). The growth inhibitory effect of somatostatin analogs is thought to be mediated through binding to somatostatin receptors expressed on neuroendocrine tumor cells (de Herder *et al.* 2003).

Two biologically active forms of somatostatin, SS-14 and SS-28, are generated from the cleavage of a pro-somatostatin peptide and bind to five high-affinity G-protein-coupled somatostatin receptor subtypes (sst 1–5) (Lamberts 1991). Pasireotide (SOM230) is a multi-ligand somatostatin analog that has high binding affinity to the somatostatin receptors sst1, sst2, sst3, and sst5 (Schmid 2008). Compared with octreotide, pasireotide has greater binding affinity for sst1, sst3, and sst5 receptors and comparable affinity for sst2 (Schmid & Schoeffter 2004). The growth inhibitory effect of somatostatin and its analogs has been linked to direct activation of somatostatin receptors, as well as to indirect effects on growth factor production (Bevan 2005, Zatelli *et al.* 2007). Binding to somatostatin receptors activates different protein tyrosine phosphatases that regulate intracellular effectors, including the

extracellular signal-regulated kinase 1/2, phosphatidylinositol 3-kinase (PI3K)/AKT, and nitric oxide synthase pathways, which leads to inhibition of cell proliferation and migration, or induction of apoptosis. Regulation of these pathways varies according to somatostatin subtype (Oberg *et al.* 2010, Bousquet *et al.* 2012). The increased binding to sst1, sst3, and sst5 by pasireotide compared with octreotide may lead to additional antiproliferative activity and increased growth inhibition.

Pasireotide has been evaluated *in vitro* in human corticotroph or somatotroph tumor cell lines, where it was found to suppress cell proliferation (Danila *et al.* 2001, Batista *et al.* 2006). Pasireotide has also been associated with inhibition of cell proliferation in cell lines derived from small intestine or pancreatic neuroendocrine tumors (Kidd *et al.* 2008). In clinical trials, pasireotide has shown preliminary evidence of efficacy in treating symptoms of hormone hypersecretion in patients with acromegaly or with octreotide-refractory carcinoid syndrome (Kvols *et al.* 2006, Petersenn *et al.* 2010). In these studies, doses of pasireotide ranged from 200 to 1200 µg s.c. twice daily. Adverse events were generally mild, and included hyperglycemia, nausea, diarrhea, and abdominal pain. A long-acting formulation, pasireotide LAR, administered monthly at doses of 40 or 60 mg resulted in drug exposure that was similar to that previously observed with the s.c. formulation at doses of 600 or 900 µg administered twice daily (Wolin *et al.* 2009). The side-effect profile of pasireotide LAR was also similar to that observed with s.c. pasireotide.

The mTOR inhibitor everolimus is also associated with antitumor activity in patients with advanced neuroendocrine tumors. In initial phase II studies, treatment with everolimus was associated with partial responses and encouraging progression-free survival durations in both pancreatic neuroendocrine tumors and carcinoid tumors (Yao *et al.* 2008, 2010). In a subsequent randomized study in pancreatic neuroendocrine tumors, treatment with everolimus was associated with a significant improvement in progression-free survival compared with placebo, leading to the approval of everolimus for this indication (Yao *et al.* 2011). In a parallel placebo-controlled study performed in advanced carcinoid tumors, treatment with everolimus and octreotide was associated with a longer progression-free survival duration compared with octreotide alone, when measured according to local investigator assessment (Pavel *et al.* 2011). These results suggest that everolimus is also associated with antitumor activity in carcinoid tumors; however, the study did

not meet its primary statistical endpoint, which mandated improvement in progression-free survival based on central radiology review.

We performed a phase 1 study evaluating the safety and feasibility of combining pasireotide and everolimus in patients with pancreatic neuroendocrine or carcinoid tumors. Cohorts of patients were treated with escalating doses of pasireotide, beginning with the s.c. twice daily formulation and, if tolerated, transitioned to the i.m. LAR formulation. In parallel, everolimus was dose escalated from 5 to 10 mg in sequential cohorts. Patients were followed for evidence of toxicity and preliminary evidence of efficacy. Treatment was continued until tumor progression, unacceptable toxicity, or withdrawal of consent.

Materials and methods

Patient population

All patients were required to be 18 years of age or older and have histologically documented, locally unresectable or metastatic carcinoid or pancreatic neuroendocrine tumors of low grade or intermediate histological grade. Patients with poorly differentiated or high-grade neuroendocrine carcinomas were not eligible. Treatment with prior chemotherapy was allowed, as was prior chemoembolization, cryotherapy, or radiofrequency ablation if measurable disease was not affected. Mandated laboratory requirements included: aspartate aminotransferase and alanine aminotransferase ≤ 3 times the upper limit of normal (ULN) (< 5 times ULN of normal if liver metastasis was present), total bilirubin ≤ 2 times ULN, serum creatinine ≤ 1.5 times ULN, absolute neutrophil count $\geq 1500/\text{mm}^3$, and platelet count $\geq 100\,000/\text{mm}^3$. All patients were required to have Eastern Cooperative Oncology Group (ECOG) performance status < 2 . Patients with uncontrolled diabetes mellitus or a fasting plasma glucose > 1.5 times ULN were excluded. Patients with a history of congestive heart failure, myocardial infarction, or unstable angina pectoris, within 6 months preceding enrollment were excluded. Patients with prolonged corrected QT interval (QTc) (> 450 ms at screening), a history of clinically significant cardiac arrhythmias, or on medications known to prolong QTc were excluded, as were patients with active or suspected chronic infections, including a history of chronic hepatitis B. All patients provided written informed consent for participation in the study, which was approved by the institutional review boards of participating institutions. The study was registered with clinicaltrials.gov (NCT00804336).

Treatment and dose escalation

Everolimus was administered orally as a once-daily dose. Pasireotide s.c. was self-administered s.c. twice daily for 4 weeks. If pasireotide s.c. was tolerated, patients received pasireotide LAR i.m. at the corresponding dose level. Pasireotide s.c. was continued for an additional 2 weeks after administration of pasireotide LAR until anticipated steady-state levels of pasireotide LAR were achieved. Pasireotide LAR was administered every 28 days. Cycles for everolimus and pasireotide LAR were repeated every 28 days. The study schema is depicted in Fig. 1. Everolimus and pasireotide were provided by the study sponsor (Novartis).

A minimum of three and a maximum of six patients were enrolled in sequential cohorts according to a standard phase I dose-escalation design. Dose escalation to the next cohort proceeded in the absence of more than one of six patients experiencing a dose-limiting toxicity (DLT). DLT was defined as grade 3 or higher non-hematological toxicity (excluding nausea, vomiting, hyperglycemia, hyperlipidemia, or alopecia), or grade 3 or higher hematological toxicity lasting ≥ 7 days. DLT was defined within the first 56 days of treatment. Once the maximum tolerated dose (MTD) was established, treatment of six additional patients at the MTD was planned to further characterize safety and toxicity.

Safety and response assessments

Patients were evaluated with a physical examination, serum chemistries, hematological parameters, and for toxicity on day 1 and day 15 of the first 28-day treatment cycle, and on day 1 of subsequent treatment cycles. Additionally, all patients were required to monitor their fasting blood glucose levels using finger stick twice daily for the first week following initiation of study drugs, with additional monitoring recommended for patients who demonstrated evidence of hyperglycemia. For patients enrolled in the expanded cohort at the maximal dose level, ECGs to

assess QTc were obtained at baseline, between 0.5 and 1.5 h after the first pasireotide s.c. injection, on day 15 of cycle 1 and on day 1 and day 22 of treatment cycles 2–4. Toxicity was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0. Serum chromogranin and fasting lipid panel were obtained at baseline and after every two treatment cycles. Tumor response was evaluated at the end of every other 28-day treatment period using multiphasic computed tomography, or magnetic resonance imaging.

Pharmacokinetics

For patients in the expanded cohort treated at the maximum dose level, blood samples were collected for pharmacokinetic monitoring. Plasma trough concentrations of everolimus were determined by liquid chromatography–mass spectrometry on cycle 2 day 1 before dosing of everolimus. Plasma trough concentrations of pasireotide were determined using immunoassay at the following time points: cycle 2 day 1 (reflecting steady-state concentration from pasireotide s.c.) and cycle 5 day 1 (reflecting steady-state concentration from pasireotide LAR).

Results

Patient characteristics

Characteristics of 22 patients enrolled in the study are listed in Table 1. The median age of the enrolled patients was 60 years, and 14 were male. Eighteen patients had carcinoid tumor, of whom most had small bowel primary tumors, and four patients had pancreatic neuroendocrine tumor. Eighteen had received prior treatment with octreotide; other prior systemic therapies included cytotoxic chemotherapy (eight patients) or biologically targeted therapies (13 patients). One patient had received prior treatment with everolimus, and one patient received prior temsirolimus.

- DLT was defined within the first 56 days of treatment.
- Dose levels are listed in Table 2.

Figure 1 Study schema.

Table 1 Patient characteristics

Characteristic	n (%)
Total patients enrolled	22
Median age (range)	60 (35–76)
Gender	
Male	14 (64%)
Female	8 (36%)
ECOG performance status	
0	16 (73%)
1 or 2	6 (27%)
Tumor subtype	
Carcinoid	18 (82%)
Small bowel	14
Bronchus	2
Unknown primary	2
Pancreatic neuroendocrine tumor	4 (18%)
Tumor histology	
Well differentiated	17 (77%)
Moderately differentiated	5 (23%)
Prior therapies	
Octreotide	18
Cytotoxic chemotherapy	8
Biologically targeted therapy ^a	13
Interferon	4
Hepatic embolization	5
Progression within 6 months before study enrollment	20 (91%)

^aPrior biologically targeted therapies included: bevacizumab (12), sunitinib (4), everolimus (1), pazopanib (1), and temsirolimus (1).

Dose-escalation and dose-limiting toxicities

The dose-escalation schema and associated DLTs are described in Table 2. No DLTs were observed in the first two patient cohorts. A single patient in cohort 3 developed grade 3 rash during the first 4 weeks of treatment. The cohort was expanded to a total of six patients with no further DLTs observed. Three patients were then enrolled in cohort 4, with one patient experiencing a DLT of grade 3 diarrhea following 2 weeks of treatment. After 2 weeks of treatment, another patient in cohort 4 developed grade 3

thrombocytopenia lasting <7 days requiring dose reduction. Although the protocol allowed enrollment of additional three patients to formally establish MTD, additional information regarding potential prolongation of the QTc interval associated with high-dose pasireotide became available during the course of the study, and the investigators, together with the sponsor, elected to suspend further enrollment and treatment at this dose level. The three patients who started treatment at dose level 4 (everolimus 10 mg p.o. qd and pasireotide 1200 µg s.c. b.i.d. followed by pasireotide LAR 80 mg i.m.) were transitioned to dose level 3, and all received pasireotide LAR 60 mg i.m. rather than the previously planned 80 mg i.m. Two patients received pasireotide 1200 µg s.c. b.i.d. with everolimus 10 mg qd for two weeks before requiring dose reduction for toxicity, and one patient received treatment at this dose level for four weeks prior dose reduction due to the protocol modification. An additional six patients were treated at dose level 3 (everolimus 10 mg p.o. qd and pasireotide 900 µg b.i.d. followed by pasireotide LAR 60 mg i.m.) in an expansion cohort, without observation of additional dose-limiting toxicities.

Exposure to treatment and clinical toxicities

Twenty-one of the 22 enrolled patients received treatment and were evaluated for toxicity. Patients received a median of six 28-day treatment cycles; only one patient discontinued treatment due to toxicity. Other reasons for treatment discontinuation included disease progression (8) or physician/patient discretion (9). Three patients remained on study at the time of data analysis.

Suspected treatment-related adverse events across all treatment cycles were consistent with the expected toxicities of both everolimus and pasireotide (Table 3). Treatment-related grade 3 and 4 adverse events included observations of grade 3 or 4 hyperglycemia

Table 2 Dosing schema and DLT summary

Dose level	Pasireotide SC b.i.d. (days 1–42; µg)	Pasireotide LAR i.m. (day 29 and every 4 weeks thereafter; mg)	Everolimus (p.o. qd; mg)	n (21 evaluated)	DLT
1	600	40	5	3	None
2	900	60	5	3	None
3	900	60	10	6+6 (expansion cohort)	Grade 3 rash (n=1)
4	1200	80 ^a	10	3	Grade 3 diarrhea (n=1)

^aDose level 4 was discontinued. Patients transitioned to dose level 3 before administration of pasireotide LAR 80 mg.

in all four dose cohorts and in a total of eight of the 21 evaluated patients (all eight with carcinoid tumor). Hyperglycemia was managed with oral hypoglycemic agents alone in two patients; the remaining six patients were treated with insulin for initial management of their hyperglycemia. Of the six patients initially treated with insulin, two patients were subsequently able to transition to oral hypoglycemic agents. Following initial observations of hyperglycemia, the protocol was amended to include a requirement for daily blood glucose monitoring during the first treatment cycle and in subsequent treatment cycles if hyperglycemia persisted.

Other grade 3–4 non-hematological toxicities were uncommon and included one patient each with mucositis, rash, diarrhea, prolonged QTc interval (>500 ms), or joint pain. Grade 3–4 hypophosphatemia was observed in six patients. Grade 3–4 hematological toxicities included thrombocytopenia (three patients) and leucopenia (two patients). Hypercholesterolemia, hypertriglyceridemia, diarrhea, and fatigue were common though mild (grade 1 or 2). We did not observe any statistically significant differences in the proportions of patients experiencing grade 3–4 toxicities or the most common overall toxicities according to tumor subtype. Grade 1–2 sinus bradycardia or QTc prolongation were each observed in two patients. In the expanded cohort of six patients treated at dose level 3, the mean baseline QTc interval

before therapy was 429 ms. The mean maximal increase in QTc interval following treatment was 11 m. In no cases were the cardiac anomalies associated with clinical sequelae.

Treatment efficacy

Patients were followed for biochemical and radiological responses with chromogranin A (CGA) levels and cross-sectional imaging studies after every 8 weeks of treatment. Nineteen patients had elevated CGA levels at baseline. Of these patients, four (21%) had a CGA level decrease of 50% or greater from baseline. Among 21 patients evaluated for radiological response, 19 (90%) experienced stable disease as their best response to therapy, and 17 (81%) experienced some degree of tumor shrinkage during the course of treatment (Fig. 2). We did not observe any differences in efficacy according to tumor type: all four patients with pancreatic neuroendocrine tumor and 16/17 patients with carcinoid tumor had a partial response or stable disease by RECIST criteria as their best response to treatment. One patient (5%) with a small bowel carcinoid tumor experienced a confirmed partial radiographical response; this patient also experienced a decrease in CGA level >50% from baseline. Two of the other patients with biochemical response experienced stable disease by RECIST associated with

Table 3 Number of patients experiencing selected adverse events by dose level

AE grade	Dose level 1 (n=3)		Dose level 2 (n=3)		Dose level 3 (n=12)		Dose level 4 (n=3)	
	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4
Non-hematological AEs								
Hyperglycemia	2	1	2	1	7	4		2
Hypercholesterolemia	3				7		1	
Hypertriglyceridemia	2		2		5		1	
Hypomagnesemia			3		5			
Hypophosphatemia		1		1	3	3	1	1
Hypocalcemia			2		6		2	
Alkaline phosphatase			1	1	5	1	1	
AST	1		1		7		2	
Fatigue	2		2		9		3	
Diarrhea	1		1		8		2	1
Nausea	2		2		9		2	
Mucositis	1		1		6	1	1	
Rash	1		1		6	1	1	
Joint pain								1
QTc prolongation					2	1	1	
Sinus bradycardia			1				1	
Hematological AEs								
Leukocytopenia	1		2		7		2	
Lymphopenia		1	1			1		
Thrombocytopenia	1		2		9	2	1	1
Anemia	2		3		8		3

Pasireotide s.c. and Pasireotide LAR Investigator's Brochure 2012, 11 Edn). This concern resulted in the discontinuation of dose level 4. As a result, no patients were treated with pasireotide LAR 80 mg and a formal MTD was not defined. While prolonged QTc was observed in four patients in our study, in no case was the QTc prolongation associated with confirmed clinical sequelae.

Both everolimus and somatostatin analogs have been associated with antitumor activity in advanced neuroendocrine tumors (Yao *et al.* 2008, 2010, 2011, Rinke *et al.* 2009). In our study, the combination of pasireotide and everolimus was associated with tumor regression in 17/21 (81%) of patients and with a RECIST-defined partial response in one patient. This value compares favorably to a 64% rate of regression associated with everolimus alone in a randomized trial of pancreatic neuroendocrine tumors (Yao *et al.* 2011). While comparisons between these studies are clearly limited by the small size of our study as well as our inclusion of patients with either pancreatic neuroendocrine tumors or carcinoid tumors, our results support further studies exploring the antitumor effect of this combination.

A variety of options exist for the management of advanced neuroendocrine tumors, including surgical, medical, and nuclear medicine strategies (Boudreaux *et al.* 2010, Kulke *et al.* 2010, Pavel *et al.* 2012). The introduction of molecularly targeted agents such as everolimus and sunitinib has expanded the treatment options available to patients. Combining everolimus with somatostatin analogs offers a promising treatment approach due to potential synergistic effects on the PI3K-mTOR pathway (Bousquet *et al.* 2012). If future studies confirm efficacy of everolimus together with pasireotide, this combination could represent an important treatment option for patients. The recommended dose for further studies based on our results is pasireotide LAR 60 mg monthly, administered in combination with everolimus 10 mg daily, which represents the dose currently approved for the treatment of pancreatic neuroendocrine tumors. We note, however, that dose escalation in our study was halted before formal determination of the MTD. It is possible that pasireotide LAR at higher doses may have greater efficacy, and further phase I dose-escalation studies of pasireotide LAR, with appropriate monitoring, are warranted.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

J A Chan has received research funding from Novartis, Bayer–Onyx, and Merck. A X Zhu has served as a consultant for Sanofi-aventis and Bristol–Myers Squibb and has received research funding from Bayer–Onyx, Imclone–Lilly. C S Fuchs has served as a consultant for Genentech, Roche, Sanofi-aventis, Pfizer, and Infinity Pharmaceuticals. M H Kulke has served as a consultant for Novartis. This work was supported by Novartis.

Acknowledgements

The authors gratefully acknowledge the support from the Saul and Gitta Kurlat fund for neuroendocrine tumor research.

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Received in final form 1 June 2012

Accepted 26 June 2012

Made available online as an Accepted Preprint
26 June 2012