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A phase I study of sirolimus and bevacizumab in patients with advanced malignancies

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ABSTRACT

Background: We performed a single institution, phase I study of sirolimus and bevacizumab, in order to determine the dose limiting toxicity (DLT) and recommended phase II doses.

Patients and methods: Eligible patients had previously treated advanced malignancies and were enrolled in three cohorts. Sirolimus 90 mg PO weekly (45 mg on days 1 and 2) was combined with bevacizumab 7.5 mg/kg (cohort #1) or bevacizumab 15 mg/kg (cohort #2) IV q3weeks. Sirolimus 4 mg PO daily was combined with bevacizumab 15 mg/kg IV q3weeks (cohort #3).

Results: Twenty-eight patients enrolled. The most common tumour types were colorectal (21%), head/neck (14%), and renal cell (11%). No DLTs were observed in cohorts #1 (4 patients) and #2 (12 patients), while two DLTs (grade 3 confusion and grade 3 fatigue) were observed in the first six patients in cohort #3 (12 patients). The most common grade 3 toxicities were fatigue (18%), hypertension (14%) and anorexia (11%). There were no responses, but one patient has had stable disease for 78 weeks.

Conclusions: The combination of sirolimus and bevacizumab at full doses is tolerable in the majority of patients. The availability and cost of sirolimus compared with other mTOR inhibitors make this an attractive agent to combine with bevacizumab.

1. Introduction

Sirolimus (rapamycin) is a naturally-occurring macrocyclic antibiotic that was discovered in 1975 and approved by the Food and Drug Administration (FDA) in 1999 for the prevention of allograft rejection after kidney transplantation.[1] After binding intracellularly to FK-506 Binding Protein 12, sirolimus inhibits the mammalian target of rapamycin (mTOR), a serine/threonine protein kinase that is a key regulator of multiple downstream proteins. Sirolimus inhibited tumour growth in preclinical models by inducing cell cycle arrest and apoptosis, leading to recognition of the mTOR pathway as a target for cancer therapy.[2,3] A phase I trial of sirolimus in patients with advanced malignancies reported a maximum tolerated dose (MTD) of 6 mg daily,[4] while another phase I trial using weekly dosing reported a MTD of 90 mg weekly.[5] Recently, sirolimus induced radiographic and clinical responses in three patients with malignant perivascular epithelioid cell tumours, a rare disease with no prior standard therapies.[6]

Despite these promising results, there has been no attempt to commercially develop sirolimus as an anticancer agent, due to its lack of patent coverage as an antineoplastic agent. Instead, analogues of sirolimus have been developed for use in oncology.[7,8] Temsirolimus, an intravenous soluble

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ester (prodrug) of sirolimus, was approved by the FDA in 2007 after a phase III trial demonstrated an overall survival benefit in renal cell carcinoma (RCC) compared with interferon alone or lower doses of the combination.[9] Everolimus, an oral mTOR inhibitor, was approved by the FDA in 2009 after a phase III trial demonstrated a progression-free survival benefit in RCC compared with placebo in patients who had failed vascular endothelial growth factor (VEGF) targeted agents.[10]

Recent and ongoing studies have explored the combined use of mTOR inhibitors and VEGF inhibitors in cancer patients, given the success of both classes of drugs independently and a strong preclinical rationale for their use in combination, although preclinical data for the combination are lacking. Bevacizumab, a monoclonal VEGF binding antibody, is approved for use in breast cancer, lung cancer, colorectal cancer, glioblastoma, and RCC. A phase II study of the combination of everolimus and bevacizumab in patients with RCC demonstrated that the combination is active and well tolerated.[11] Since sirolimus is commercially available and relatively inexpensive (at least compared to temsirolimus and everolimus), we aimed to determine the dose-limiting toxicity (DLT) and recommended phase II doses (RPTD) for the combination of sirolimus and bevacizumab. This phase I trial was registered at ClinicalTrials.gov under the identifier NCT00667485.

2. Patients and methods

2.1. Eligibility

Patients were eligible if they were 18 years of age or older with pathologically confirmed advanced solid tumours for which standard curative or palliative measures either do not exist or were no longer effective. They were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, as well as adequate organ and marrow function. Measurable disease was not required.

Prior treatment with an mTOR inhibitor (including sirolimus) or with bevacizumab was allowed, but prior therapy with a combination of the two was not allowed. Due to the known bleeding risk associated with bevacizumab, patients with squamous non-small cell lung cancer were excluded. Given the absence of data at the time of trial design regarding other patients with potentially higher bleeding risk, also excluded were patients with lung cancer or lung metastases who were taking full dose anticoagulation, aspirin at a dose >325 mg daily, or non-steroidal anti-inflammatory drugs.

The protocol was reviewed by the institutional review board and all patients provided written informed consent.

2.2. Study design and treatments

The primary objective of the study was to determine the safety and tolerability of the combination of sirolimus and bevacizumab, in order to identify the DLT and RPTD. As such, the primary end-point was toxicity. Secondary end-points included tumour response and pharmacokinetics of sirolimus. Since efficacy was not a primary end-point, correlative studies to identify potential biomarkers were not incorporated into the design. Patients were enrolled in three sequential dosing cohorts, using starting doses of sirolimus derived from earlier phase 1 studies.[4,5] In cohort #1, patients received sirolimus 90 mg PO weekly (45 mg on days 1 and 2) and bevacizumab 7.5 mg/kg IV q3weeks. In cohort #2, the bevacizumab dose was escalated to 15 mg/kg IV q3weeks. In cohort #3, patients received sirolimus 4 mg PO daily and bevacizumab 15 mg/kg IV q3weeks. Sirolimus was administered using a 1 mg/mL oral solution for cohorts #1 and 2, and using 1 mg or 2 mg tablets for cohort #3. Patients fasted for 2 hours before and 1 hour after taking sirolimus, in order to avoid the known effect of food on oral bioavailability.[12]

2.3. Assessments

Evaluations before and during treatment included a complete medical history and physical examinations, haematologic and metabolic laboratory profiles, urine protein and toxicity assessments according to the National Cancer Institute Common Toxicity Criteria (version 3.0). Tumour responses were categorised as complete responses, partial responses, stable disease or progressive disease according to the Response Evaluation Criteria in Solid Tumours (RECIST, 1.0).[13]

2.4. Dose modifications

Patients experiencing toxicity $\geqslant$ grade 3 attributable to sirolimus had treatment held until resolution of toxicity to $\leqslant$ grade 1, then restarted therapy at a 25% dose reduction. If toxicity $\geqslant$ grade 3 developed upon re-challenge, patients were taken off study. For grade 2 toxicity that recurred after re-challenge with dose reduction, and was subjectively intolerant and long-standing, a further 25% dose reduction was allowed. Any patient requiring more than 2 dose reductions or with unresolved toxicity after 3 weeks was taken off study. No dose modifications were allowed for bevacizumab. Bevacizumab was held for grade 3 proteinuria, while patients were taken off study for more serious grade 3 toxicities attributable to the drug.

2.5. Definition of DLT

Haematologic DLT included Grade 4 neutropenia (ANC < 500 lasting more than 5 days, or with concomitant fever > 38.5 degrees celsius, or with sepsis or other severe infection) or Grade 4 thrombocytopenia. Non-haematologic DLT included any grade 3 or grade 4 adverse event (at least possibly attributable to therapy), except the following: untreated nausea/vomiting, hypersensitivity reactions, Grade 3 hypertension, or Grade 3 proteinuria. Any adverse effect resulting in delay of administration of a subsequent dose of sirolimus or bevacizumab exceeding 3 weeks was also considered a DLT.

2.6. Pharmacokinetic studies

Samples for pharmacokinetic analysis of sirolimus were collected on day 1 of cycle 1 at four different time points: before the dose, and 1, 2 and 4 hours after the dose. These time points were selected in order to capture the observed maximum concentration (C_{max}), since a prior study in renal transplant patients showed that the time to peak blood concentration after oral administration was 1.4 ± 1.2 hours.[14]

2.7. Specimen collection

Approximately 3–4 mL of whole blood was collected into an EDTA-containing vacutainer. All patient samples were collected in tubes labelled with the patient's full name, the date and the time of the sample collection. Samples were frozen for later use.

2.8. Pharmacokinetic analysis

Sirolimus whole blood concentrations for each patient at each time point were measured using liquid chromatography–mass spectrometry and quantified using a standard curve. Observed C_{max} was used to determine whether concentrations were roughly similar to those observed with sirolimus alone in previous studies.

3. Results

3.1. Patient characteristics

Baseline demographics and tumour types of the 28 enrolled patients are presented in Table 1. Four patients enrolled in cohort #1, 12 in cohort #2, and 12 in cohort #3. The most common tumour types were colorectal (21%), head/neck (14%), and RCC (11%). A total of 101 3-week cycles were administered (median per patient, 4; range 1–22).

3.2. Toxicity

Table 2 summarises the clinically relevant grades 1–3 toxicities that were at least possibly related to study drugs and that were observed in at least 4 (of 28 total) patients. No DLTs were observed in cohorts #1 and #2. For cohort #3, one DLT (grade 3 confusion) was observed in the first 3 patients. The cohort was expanded to 6 patients, and another DLT (grade 3 fatigue) was observed. The cohort was further expanded to 12, and two additional grade 3 toxicities were observed (fatigue and elevated transaminases). The most common grade 3 toxicities that were at least possibly related to study drugs were fatigue (18%), hypertension (14%), anorexia (11%) and diarrhoea (8%). One patient in cohort #3 developed grade 4 hypoxemic respiratory failure that was possibly related to sirolimus during the first week of therapy, with CT scan showing diffuse airspace opacities consistent with Acute Respiratory Distress Syndrome (ARDS). The etiology of his respiratory failure and CT findings could not be further elucidated, as the patient declined bronchoscopy and, after recovering, elected to go off study. Sirolimus was held and/or dose reduced in 5 of 12 patients (42%) in cohort #2, for the following reasons: Grade 3 fatigue; Grade 3 diarrhoea; Grade 3 hypertension and Grade 2 neutropenia; Grade 2 esophagitis; and Grade 3 fatigue/anorexia/diarrhoea. Sirolimus was held and/or dose reduced in 4 of 12 patients (33%) in cohort #3, for the following reasons: Grade 3 dyspnea; Grade 3 fatigue followed by Grade 4 respiratory failure (as above); Grade 3 fatigue; and Grade 3 elevated transaminases followed by Grade 2 fatigue (two dose reductions).

3.3. Efficacy

Fig. 1 is a waterfall plot that shows the best responses for each of the 19 patients who were evaluable for response. There were no responses by RECIST, but one patient with Hurthle

Table 1 – Baseline demographics and tumour types for the 28 enrolled patients. Race: W = white; B = black; H = hispanic.

Patient #	Dose cohort	Tumour type	Age	ECOG PS	Gender	Race
1	1	Endometrial	58	0	F	W
2	1	Urothelial	65	1	M	W
3	1	Small round blue cell tumour	47	1	F	W
4	1	Prostate	75	1	M	W
5	2	Adrenocortical	40	1	M	W
6	2	Prostate	79	0	M	W
7	2	Sarcoma	66	1	M	W
8	2	Cervical	42	0	F	W
9	2	Atypical carcinoid of lung	76	1	F	W
10	2	Renal cell	52	0	F	W
11	2	Ovarian	52	0	F	W
12	2	Rectal	62	1	F	W
13	2	Head & neck	53	0	M	W
14	2	Colon	60	0	F	W
15	2	Renal cell	73	1	M	W
16	2	Appendiceal	56	1	M	W
17	3	Breast	48	1	F	B
18	3	Oesophageal	70	1	F	W
19	3	Rectal	59	0	M	W
20	3	Colon	63	1	M	H
21	3	Urothelial	52	0	F	W
22	3	Head & neck	56	1	M	W
23	3	Thyroid	48	0	M	W
24	3	Adenocystic	68	1	F	W
25	3	Renal cell	66	1	M	W
26	3	Colon	67	0	M	W
27	3	Neuroendocrine	68	0	M	W
28	3	Endometrial	61	0	F	W

Table 2 – Clinically relevant, Grade 1–3 toxicities that were at least possibly related to study drugs and that occurred in at least 4 (of 28 total) patients.

	Grade 1		Grade 2		Grade 3	
	#	%	#	%	#	%
Cohort #1 (n = 4)						
Haematologic						
Leukopenia/neutropenia	1	25	1	25	0	0
Thrombocytopenia	2	50	0	0	0	0
Anaemia	0	0	1	25	0	0
Non-haematologic						
Anorexia	2	50	0	0	0	0
Diarrhoea	2	50	0	0	0	0
Fatigue	0	0	2	50	1	25
Hypercholesterolaemia	3	75	0	0	0	0
Hyperglycaemia	3	75	0	0	0	0
Hypertriglyceridemia	1	25	2	50	1	25
Mucositis/stomatitis	2	50	1	25	0	0
Nausea/vomiting	3	75	0	0	0	0
Cohort # 2 (n = 12)						
Haematologic						
Leukopenia/neutropenia	3	25	3	25	0	0
Thrombocytopenia	4	33	0	0	0	0
Anaemia	0	0	2	17	0	0
Non-haematologic						
Anorexia	6	50	2	17	2	17
Diarrhoea	6	50	3	25	2	17
Fatigue	4	33	4	33	2	17
Fever	2	17	0	0	0	0
Hypercholesterolaemia	4	33	3	25	0	0
Hyperglycaemia	3	25	1	8	0	0
Hypertension	0	0	0	0	3	25
Hypertriglyceridemia	0	0	5	42	0	0
Mucositis/stomatitis	4	33	2	17	0	0
Nausea/vomiting	7	58	4	33	0	0
Dry skin/rash/pruritis	3	25	1	8	0	0
Weight loss	1	8	1	8	0	0
Cohort # 3 (n = 12)						
Haematologic						
Leukopenia/neutropenia	4	33	1	8	1	8
Thrombocytopenia	3	25	1	8	0	0
Anaemia	1	8	1	8	0	0
Non-haematologic						
Anorexia	4	33	1	8	1	8
Diarrhoea	5	42	2	17	0	0
Fatigue	5	42	3	25	2	17
Fever	2	17	1	8	0	0
Hypercholesterolaemia	4	33	2	17	0	0
Hyperglycaemia	2	17	1	8	0	0
Hypertension	0	0	1	8	1	8
Hypertriglyceridemia	3	25	0	0	0	0
Mucositis/stomatitis	4	33	1	8	0	0
Nausea/vomiting	4	33	1	8	0	0
Dry skin/rash/pruritis	4	33	0	0	0	0
Weight loss	3	25	0	0	0	0

cell thyroid cancer has had stable disease (with 24% maximal tumour reduction) after 78 weeks and remains on study (as of February 21, 2011). The mean ± SD percent change in tumour size at best response was −4.1 ± 13.3%, based on these 19 patients.

3.4. *Pharmacokinetic data*

Mean C_{max} ± SD was 102.9 ± 29.1 ng/mL for the 4 patients in cohort #1, 83.1 ± 41.2 ng/mL for the 12 patients in cohort #2, and 9.2 ± 8.2 ng/mL for the 12 patients in cohort #3.

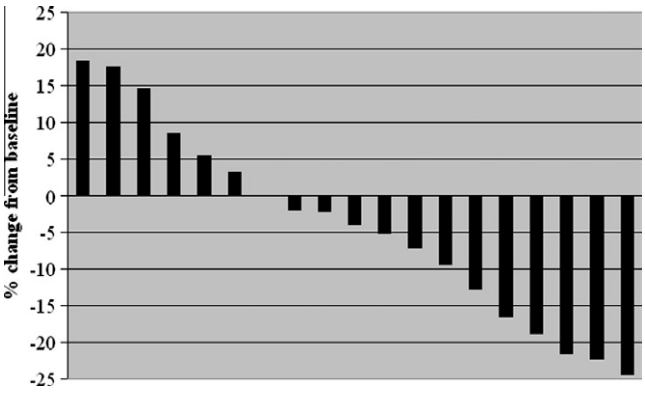

Fig. 1 – Waterfall plot showing best tumour size response (by RECIST) for each of the 19 patients who were evaluable for response.

4. Discussion

Many studies are ongoing to explore whether the combination of mTOR and VEGF pathway inhibition might prove effective in treating patients with advanced malignancies. Preliminary results reported from a randomised phase II trial of temsirolimus and bevacizumab in metastatic RCC showed more toxicity for the combination than in the sunitinib or bevacizumab/IFN-α arms, and no evidence of synergistic/additive efficacy.[15] In contrast, preliminary results recently reported from a phase II trial of everolimus and bevacizumab in refractory metastatic colorectal cancer showed reasonable tolerability and promising efficacy, including a suggestion that the combination might overcome resistance to bevacizumab.[16] There is an ongoing phase I study of sirolimus and bevacizumab in patients with unresectable hepatocellular carcinoma[17]; ongoing studies of temsirolimus and bevacizumab in prostate cancer,[18] endometrial cancer,[19] and glioblastoma multiforme[20]; and ongoing studies of everolimus and bevacizumab in ovarian cancer[21] and RCC.[22]

We designed the current study using sirolimus as the mTOR inhibitor because it is commercially available, oral, has a long safety record, and is relatively inexpensive. Sirolimus at a dose of 4 mg daily would cost roughly $1400/month, which is approximately 5-fold less than the monthly cost of everolimus or temsirolimus at currently approved doses for RCC,[23] since it is marketed as an immunosuppressant rather than an oncology agent. Furthermore, the cost of sirolimus is likely to decrease dramatically when its sole remaining use patent (US patent #5,100,899) expires in 2013, since that should permit the marketing of generic versions of sirolimus.

In the current study, we found that the combination of sirolimus and bevacizumab is tolerable in the majority of patients, even when the drugs are combined at full doses. We explored two different dosing regimens of sirolimus, 90 mg weekly and 4 mg daily, and found that either could be combined with full dose bevacizumab (15 mg/kg IV q3weeks) with 42% and 33% of patients experiencing Grade 3/4 toxicity, respectively, which is comparable to 36% of patients who had grade 3/4 toxicity with the combination of temsirolimus and bevacizumab.[15] Fatigue was the most common Grade 3 toxicity, and can occasionally be dose-limiting, which is a known adverse effect of the mTOR inhibitors. Altered glucose and lipid metabolism, another class effect of mTOR inhibitors, were frequently observed but typically mild (Grade 1 or 2). Non-infectious pneumonitis and opportunistic infections were not definitely observed, although either (or both) may have contributed to the one case of Grade 4 respiratory failure. It is worth noting that gastrointestinal toxicities, including nausea/vomiting and diarrhoea, were both more common and more severe in the cohorts with weekly sirolimus. Interestingly, we observed no Grade 3 proteinuria or mucositis in any of the cohorts, while these were the most common Grade 3 toxicities reported in RCC patients receiving everolimus and bevacizumab.[11]

The interindividual variability in C_{max} is consistent with what has been observed in other studies with sirolimus.[4,24,25] C_{max} did not correlate with toxicity, which is not surprising since data in the transplant literature suggest that trough levels (rather than C_{max}) correlate most reliably with toxicity.[26] Mean C_{max} with intravenous dosing of sirolimus in our study was comparable to the mean C_{max} for the sirolimus metabolite after a single intravenous dose of temsirolimus 25 mg.[27] Although no RECIST responses were observed amongst the 19 patients who were evaluable for response, it is encouraging that three patients had >20% reduction in tumour size at the time of best response, one of whom continues to have stable disease after 78 weeks.

Based on the independent success of mTOR inhibitors and VEGF inhibitors in treating advanced RCC, a randomised phase II trial of sirolimus and bevacizumab (versus either bevacizumab alone, or in combination with interferon alpha) in advanced RCC would be a logical next step. Considering the above list of ongoing trials with bevacizumab and an mTOR inhibitor in other tumour types, it would also be reasonable to study the combination of sirolimus and bevacizumab in any disease for which the results of current trials are promising. If and when such trials are conducted, the recommended doses for use in phase II studies are sirolimus 90 mg weekly (in two divided doses on consecutive days) or 4 mg daily, in combination with bevacizumab 15 mg/kg IV q3weeks.

Role of the funding source

Genentech provided financial support for the trial, but did not have any role in the acquisition of data, analysis/interpretation of data, or preparation of the manuscript.

Conflict of interest statement

Dr. Fleming has received funding in the past to conduct clinical trials with temsirolimus (a competitor to sirolimus). Dr. Stadler has received consulting income from advisory boards (<$10,000/year) to give advice on the development and commercialisation of everolimus (a competitor to sirolimus) for Novartis and bevacizumab for Genentech/Roche. Dr. Ratain has been compensated for consulting on behalf of Genentech, Hoffman–La Roche, and Pfizer; and has also received grant funding from Genentech and Novartis.

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