Phase Ib of Sorafenib in Combination With Everolimus in Patients With Advanced Solid Tumors, Selected on the Basis of Molecular Targets

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AUTHOR SUMMARY

ABSTRACT

Background. Molecular alterations of the PI3K and Ras pathways often occur in human cancer. In this trial, the pharmacokinetics, toxicity, and activity of two drugs inhibiting these pathways—everolimus and sorafenib—were investigated.

Methods. Thirteen patients with progressing solid tumors were treated with everolimus and sorafenib, according to a 3+3 scheme. Patients were selected on the basis of immunohistochemical expression of tumor molecular targets, including phospho-AKT, -p70S6K, and -ERK1/2.

Results. The daily recommended dose identified was 2.5 mg of everolimus and 600 mg of sorafenib. Dose-limiting toxicities included grade 3 asthenia and hand-foot skin reaction. No grade 4 adverse events were observed. The most frequent grade 3 toxicities were hypophosphatemia (30.8%), alanine aminotransferase level increase, asthenia, and anorexia (14%). No pharmacokinetic interactions were identified between everolimus and sorafenib. Of 12 evaluable patients, we observed 2 partial responses, with greater than 10% shrinkage in an additional 5 patients. Objective responses were observed in one patient with a thymoma and in one patient with a lung adenocarcinoma. Tumor shrinkage that did not qualify as a partial response was seen in an abdominal leiomyosarcoma and in adenoid cystic carcinomas.

Conclusion. The combination of everolimus and sorafenib is safe. The tumor activity observed in different tumor types could be the result of the combined action of these drugs as well as the molecular selection of the treated population. Further research is warranted to better investigate drugs simultaneously blocking the PI3K and the Ras pathways and to refine patient selection. *The Oncologist* 2014;19:344–345

Figure 1. Percentage of tumor reduction.

DISCUSSION

This phase I study demonstrated that everolimus and sorafenib can be safely associated at daily doses of 2.5 mg of everolimus and 600 mg of sorafenib. In addition, the combination has shown signs of antitumor activity in a small population selected on the basis of specific molecular tumor targets (Fig. 1).

Initially, sorafenib was administered at a dose of 800 mg daily and everolimus at 2.5 mg daily, but the toxicity experienced, which was mainly ascribed to sorafenib, led to a reduction of sorafenib to 600 mg daily. At this new dose level, the combination was better tolerated and all toxicities were managed with short periods of drug interruption. The most frequent grade 3 toxicities overlapped with those described in other studies exploring the same combination

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Table 1. Efficacy

Patient ^a	Tumor type	Tumor response	Volume reduction (%)	PFS (days)
1	GIST	PD ^b	+5	70
2	Lung ADK	PR	−34	126
3	Thymoma	PR	−81	146
4	Leiomyosarcoma	SD	−5	136
5	Adenoid cystic CA	SD	−15	252
6	Adenoid cystic CA	SD	−4	183
7	Leiomyosarcoma	SD	+0.9	711
8	Adenoid cystic CA	SD	−25	328
9	Parotid ADK	SD	−6	310
10	Thymoma	SD	−4.4	86
11	Lung ADK	SD	−27	155
12	Lung pleomorphic CA	PD	+41	61

^aPatients 1–4: Level 1 pre-amendment. Patients 5–10: Level 1 post-amendment. Patients 11 and 12: Level 2 post-amendment.

^bClinical progression.

Drug activity evaluated as RECIST response, percentage of tumor volume reduction, and progression-free survival, according to histology and dose level. Abbreviations: ADK, adenocarcinoma; CA, carcinoma; GIST, gastrointestinal stromal tumor; PFS, progression-free survival; PD, progressing disease; PR, partial response; SD, stable disease.

or a similar combination of targeted agents. A majority of patients had reductions in the sorafenib dose, treatment interruptions, or both but usually were able to resume treatment. In our opinion, the toxicity profile cannot be ascribed to pharmacokinetic (PK) interactions. Although the PK information from this study is limited by the small sample size, we did not observe any modification of the PK profile of everolimus in association with sorafenib.

In terms of efficacy, partial responses were observed in one thymoma and one lung adenocarcinoma (Table 1). In addition, a second patient with a diagnosis of lung adenocarcinomas enrolled in the study had some tumor reduction. It is noteworthy that clinical trials with sorafenib or everolimus as single agents in non-small cell lung cancer have shown some antitumor activity. Consequently, although it is possible that the activity we observed could reside in the combination of the two drugs and/or the selection of the patients, we

cannot exclude the possibility that it is caused by either of the agents alone.

Interestingly, other signs of activity were found in tumor types that are minimally responsive to chemotherapy, such as adenoid cystic carcinomas and abdominal leiomyosarcoma, the former being a tumor in which sorafenib has been previously reported to cause tumor shrinkage.

Although definitive conclusions of efficacy cannot be drawn in phase I studies, the combination did cause reduction in tumor size. This could be related to positive interaction of everolimus and sorafenib, specific selection of the patients, or activity of the individual agents. Further research is warranted to investigate the efficacy of drugs simultaneously blocking the PI3K and the Ras pathways and the effect of the molecular selection of the patients.

Author disclosures available online.