Sorafenib has clinical activity against metastatic papillary thyroid cancer but requires close monitoring and aggressive management of drug toxicity


**SUMMARY**

**BACKGROUND** This phase II clinical trial of sorafenib is based on the central role of the Ras-Raf-MAP-ERK signaling pathway and vascular endothelial growth factor (VEGF) in papillary thyroid cancer (PTC). Although sorafenib was initially considered to be a selective RAF kinase inhibitor, it is now known to be a multitarget inhibitor that targets several receptor tyrosine kinases at submicromolar concentrations, including VEGF receptors (VEGFRs) 1 to 3 and platelet-derived growth factor receptor.

**METHODS** The primary end point of the study was the objective response rate. Secondary end points were the correlation of serum thyroglobulin (Tg), functional imaging, tumor genotype, and signaling inhibition in tumor biopsies. The study used a Simon minimax two-stage design. In a typical two-stage design of a phase II clinical trial of cancer, a fixed number of patients are initially enrolled. The trial may be terminated for lack of therapeutic efficacy if the number of treatment successes after the first stage is too small. If so, an additional fixed number of patients are enrolled to accumulate additional information on efficacy. Accrual to arm B in the Kloos study was designed to stop as soon as arm A was fully accrued. The study subjects were patients who were 18 years of age or older with adequate performance status and measurable tumor. Treatment with chemotherapy or radiation therapy was not permitted within 4 weeks before entry into the study, and radiiodine therapy (with $^{131}$I) was not allowed within 24 weeks before entry into the study, or within 4 weeks if the patient had a negative posttreatment $^{131}$I scan. Also required were a leukocyte level ≥3000/L, an absolute neutrophil count ≥1500/L, a platelet count ≥100,000/μL, and serum bilirubin, aspartate aminotransferase and alanine aminotransferase, and creatinine levels 1.5-fold the upper limit of normal. To study the effects on tumor perfusion, dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) scans were obtained within 4 weeks before and every 8 weeks while on therapy, and fluorodeoxyglucose positron-emission tomography scans were obtained at similar time points when possible.

Patients were observed every 4 weeks for 1 year and if stable, every 12 weeks thereafter. Therapy was withheld if the patients had a grade ≥3 or recurrent grade ≥2 drug-related toxicity other than hematologic toxicity, or a grade ≥2 hand-foot-skin reaction until the toxicity resolved to grade ≤1. Sorafenib was generally tolerated; however, a dose reduction to 600 or 400 mg/day of sorafenib and a subsequent dose reescalation up to 800 mg/day was allowed. Sorafenib was continued until one of the following occurred: progressive disease, patient off sorafenib longer than 24 consecutive days for any reason, intercurrent illness that prevented further therapy, unacceptable adverse events, or patient withdrawal from the study. The response was assessed every 2 months using the Response Evaluation Criteria in Solid Tumors (RECIST) (Figure 1).

**RESULTS** A total of 56 patients were selected for study; 31 (55%) were men and 25 (44%) were women. The median age of the patients in arm A was 67 years (range, 33 to 90), and in arm B 56 years (range, 27 to 76). In all, 41 (73%) had PTC, 19 (46%) of whom were in arm A and 22 (54%) in arm B.
EDITOR’S CHOICE — THYROID CANCER

Kloos RT, et. al.

Thirty patients (73%) had classic PTC, 5 (12%) had follicular variant PTC, 4 (10%) had tall-cell-variant PTC, and 2 (5%) had poorly differentiated PTC. The distribution of tumor histologies in both arms of the study is shown in Figure 2. Two patients (4%) had follicular thyroid cancer (FTC), 9 (16%) had Hürthle-cell carcinoma, and 4 (7%) had anaplastic thyroid cancer. Arm A comprised 19 patients with PTC and 2 with FTC; arm B comprised 22 patients with PTC, 2 with FTC, 9 with Hürthle-cell carcinoma, and 4 with anaplastic thyroid cancer. The site of tumor metastases is shown in Figure 3.

TREATMENT ADMINISTERED The median duration of therapy was 14 months in arm A patients and 10, 8, and 2 months in patients with PTC, HTC/FTC, and ATC in arm B, respectively (Figure 4). Common grade 3 adverse events included hand-foot-skin reaction and musculoskeletal pain and fatigue. The reasons for dose reduction were hand-foot-skin reaction, diarrhea and weight loss, hypertension, fatigue, arthralgia, musculoskeletal chest pain, and mouth pain.

TUMOR RESPONSE ACCORDING TO RECIST

Of 41 patients with PTC, 6 had a partial response (PR; 15%; 95% confidence interval [CI], 6 to 29) and 23 (56%; 95% CI, 40 to 72) had stable disease for longer than 6 months. Median duration of PR was 7.5 months (range, 6 to 14). Median progression-free survival was 15 months (95% CI, 10 to 27.5) (Figures 5, 6 and 7).

BRAF mutation was detected in 17 (77%) of the 22 PTCs that were analyzed. Four of 10 paired tumor biopsies showed a reduction in VEGFR phosphorylation levels, ERK phosphorylation, and in VEGF expression during sorafenib therapy. No partial responses were noted among non-PTC patients. Clinical adverse events are shown in Figure 8.

Figure 3. Site of tumor metastases in arms A and B. (Derived from data in Table 1 of Kloos et al.)

Figure 4. This is a summary of sorafenib treatment administered and the median duration of therapy and the median time to dose reductions (derived from data in Table 2 of Kloos et al.).

Figure 5. Tumor response is measured according to the RECIST (Response Evaluation Criteria in Solid Tumors).

Figure 6. This shows the best thyroglobulin response to therapy.
SERUM THYROGLOBULIN CHANGES

In 14 of 18 patients (78%) the serum Tg was assessable, and declined more than 25% (Figure 6). In 10 of 14 assessable patients with PTC (71%), the 8- or 16-week DCE-MRI scans showed a median decrease of 46% (range, 27 to 92) during therapy, whereas no change was noted in the remaining four patients, none of whom had an objective response as compared with baseline. Among eight patients who had assessable results for paired biopsies and serial DCE-MRIs, there was no correlation between VEGFR levels or signaling response of VEGFR and pharmacokinetic parameters of DCE-MRI measurements.

CONCLUSION

Sorafenib is relatively well-tolerated, with clinical and biologic antitumor activity in patients with metastatic papillary thyroid cancer, but it requires close surveillance and aggressive management of drug toxicity.
from patients with PTC showed a reduction in the levels of vascular VEGF phosphorylation, ERK phosphorylation, and VEGF expression during sorafenib therapy. No partial responses were found among patients with other forms of thyroid cancer. Stable disease and partial responses suggest a greater clinical benefit than that based on partial responses and stable disease of 6 months or more in 23 patients with PTC. Also, a better response is inferred from the serum Tg response.

Although the dose schedule used in this study was generally well tolerated, dose reductions were necessary in about half the patients. The authors suggest that the higher frequency of dose reductions in their study might be a result of relatively lower acceptability of long-term toxicities by patients with thyroid cancer. Still, the tumor response was generally maintained despite dose reductions.

Endocrinologists are not widely trained in the use of these drugs, but this study shows that the drug has benefits but also important complications. Physicians using these drugs must be aware of the adverse events of the drug and capable of quickly responding to this problem.

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References
