Objective responses to motesanib are low in patients with medullary thyroid carcinoma, but the disease becomes stable in most patients while receiving the drug

Schlumberger MJ, Elisei R, Bastholt L, Wirth LJ, Martins RG, Locati LD, Jarzab B, Pacini F, Daumerie C, Droz JP, Eschenberg MJ, Sun YN, Juan T, Stepan DE, and Sherman SI. Phasell Study of Safety and Efficacy of Motesanib in Patients with Progressive or Symptomatic, Advanced or Metastatic Medullary Thyroid Cancer. J Clin Oncol 2009; 27:3794-3801.

SUMMARY

BACKGROUND

The current treatment for medullary thyroid carcinoma (MTC) includes total thyroidectomy with removal of involved metastatic lymph nodes. External beam radiotherapy may also be employed in conjunction with surgery for locoregional disease control. Patients with distant metastases, however, present a challenge to physicians because standard chemotherapeutic regimens are largely ineffective for controlling disease progression. The introduction of targeted molecular therapies aimed at various steps in the oncogenic pathway has renewed hope for the discovery of an agent with the potential to control advanced or progressive MTC. Motesanib, an inhibitor of vascular endothelial growth factor receptors (VEGFR 1-3), platelet derived growth factor (PDGF), and Kit, has been shown to inhibit wild type RET in vitro and induced a partial response in one MTC patient during a phase I trial. The current study seeks to examine the efficacy and tolerability of motesanib in patients with progressive or symptomatic, locally advanced or metastatic MTC.

METHODS

This was an international phase II open-label, single-arm trial, the primary endpoint of which was an objective response by Response Evaluation Criteria in Solid Tumors (RECIST). Additional parameters evaluated were the duration of response, progression-free survival, tumor-related symptoms, and time to response, overall survival time, changes in tumor markers, pharmacokinetics, and safety. Patients were given motesanib 125mg orally once daily until disease progression or unacceptable toxicity occurred. Subjects eligible for the study were adults with locally advanced or metastatic MTC with either disease progression in the 6 months prior to study entry or with symptomatic disease such as MTC-related diarrhea with or without flushing. Also, patients were required to have at least one measurable lesion per RECIST and tumor not amenable to surgery, external beam radiation, or other local therapies. Disease progression was based on radiographic images utilizing RECIST. Excluded from the study were patients with Eastern Cooperative Oncology Group (ECOG) performance scores ≥2, inadequate renal, hepatic, or cardiac function, or previous treatment with motesanib, or with RET or VEGF inhibitors. Patients were given motesanib 125mg orally once daily for up to 48 weeks, or until disease progression or unacceptable toxicity occurs.

Imaging with CT or MR was performed every 8 weeks and when disease progression was suspected. Blood samples were collected from 10 patients after 0.25, 0.5, 1, 2, 4, 6, 8, and 24 hours after the first dose of motesanib. Trough levels were also checked in all patients before their scheduled dose every 4 weeks. Serum calcitonin and CEA levels were followed at baseline and every 4 weeks. Tumor-related symptoms were monitored by administration of a questionnaire at baseline and every 8 weeks.

RESULTS

Ninety-one patients received at least one dose of motesanib, most of whom had sporadic MTC (84%). The median baseline calcitonin was 22,489ng/L and the CEA was 114µg/L. Motesanib was discontinued early in 54 patients before study completion because of disease progression in 30, adverse events in 13, death in 3, and for various other reasons in 8 patients. The median treatment duration was 38 weeks.

Responses to motesanib (Figure 1)

A confirmed partial response (PR) was seen in 2 patients according to RECIST; there were no complete responses seen. The majority of patients (n=74, 81%) had stable disease (SD), 44 of whom had durable SD ≥ 24 weeks (48%). A decrease in target lesion measurement from baseline was seen in 69 (76%) patients. Median progression-free survival was 48 weeks; overall survival at 12 months was 75%. Twenty-four patients died during the study period. An extension study was created for 34 patients who completed the 48-week therapy protocol.

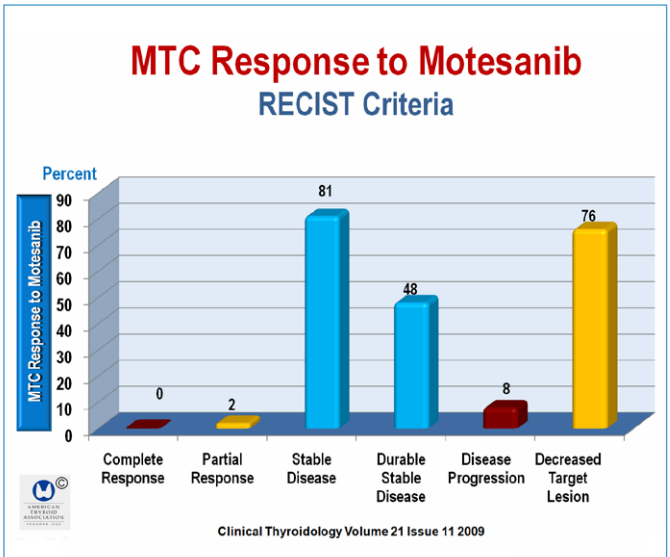

Figure 1. This figure shows the response to motesanib in patients with medullary thyroid carcinoma. RECIST = Response Evaluation Criteria in Solid Tumors. Disease Progression in 8% is the best response in this group. A decrease in target lesion measurement from baseline was seen in 69 (76%) patients. Figure derived from data in Table 2 of Schlumberger et al.

A total of 78 patients had a baseline and at least one post-baseline assessment of tumor related-symptoms. Of this group, 55 reported diarrhea at baseline. By week 16, the mean rate (±SE) of diarrhea frequency decreased significantly to (4.1±0.5 episodes/d) as compared with the number of baseline of (5.2±0.4 episodes/d; P = 004). Still, by week 48, this group reported (5.1±0.7) episodes/d; P = 0.5) or any other times between weeks 16 through 48. Among the 18 patients without self-reported diarrhea at baseline, the frequency of diarrhea increased from 0 at baseline to 1 to 3 episodes/d at week 24, and increased significantly by week 32 to (5.4±7 episodes/d; P = 0.02), and stayed elevated at 1 to 3 episodes/d for the remainder of the study.

Adverse events to motesanib (Figures 2 to 4)

The majority of patients (88%) had at least one motesanib-related adverse event. The most commonly encountered were diarrhea (41%), fatigue (41%), hypertension (27%), anorexia (27%), and nausea (26%). There were 35 grade 3 events and 3 patients experienced a grade 4 adverse event. Of particular note, acute gallbladder toxicity was seen in 8 patients, which included 3 with cholecystitis, 3 with cholelithiasis, and 1 with gallbladder enlargement. In addition, elevated TSH levels were found in 37 patients (41%).

Pharmacokinetics

The pharmacokinetics revealed motesanib was rapidly absorbed.

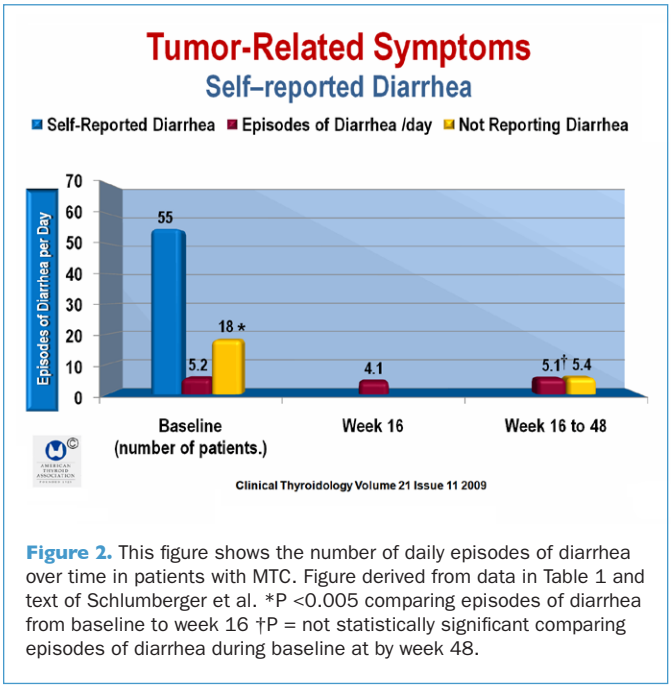

Figure 2. This figure shows the number of daily episodes of diarrhea over time in patients with MTC. Figure derived from data in Table 1 and text of Schlumberger et al. *P <0.005 comparing episodes of diarrhea from baseline to week 16 †P = not statistically significant comparing episodes of diarrhea during baseline at by week 48.

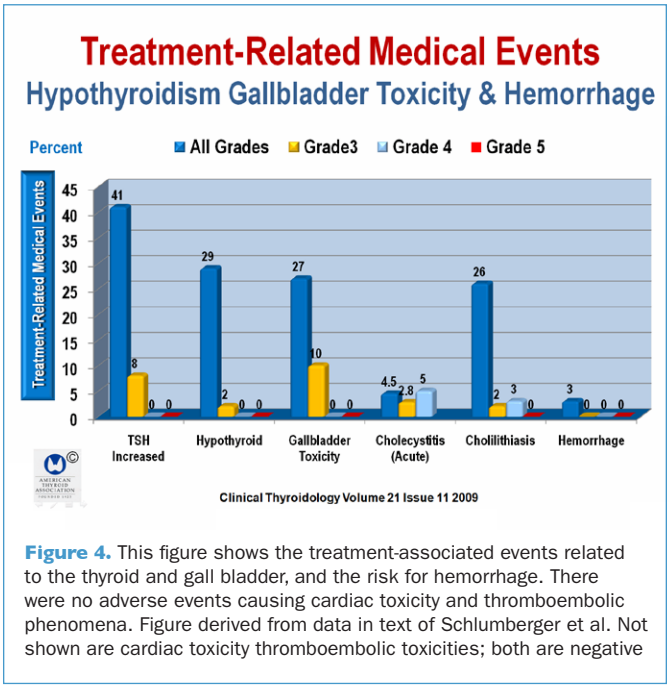

Figure 4. This figure shows the treatment-associated events related to the thyroid and gall bladder, and the risk for hemorrhage. There were no adverse events causing cardiac toxicity and thromboembolic phenomena. Figure derived from data in text of Schlumberger et al. Not shown are cardiac toxicity thromboembolic toxicities; both are negative

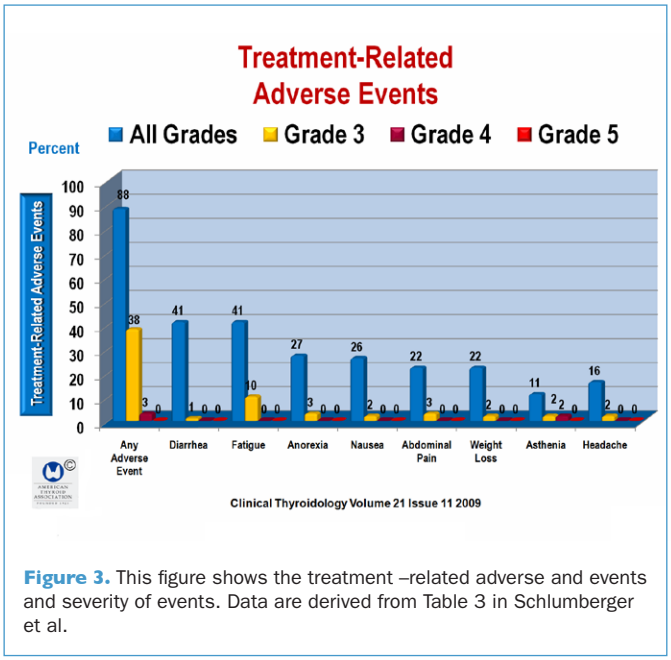

Figure 3. This figure shows the treatment –related adverse and events and severity of events. Data are derived from Table 3 in Schlumberger et al.

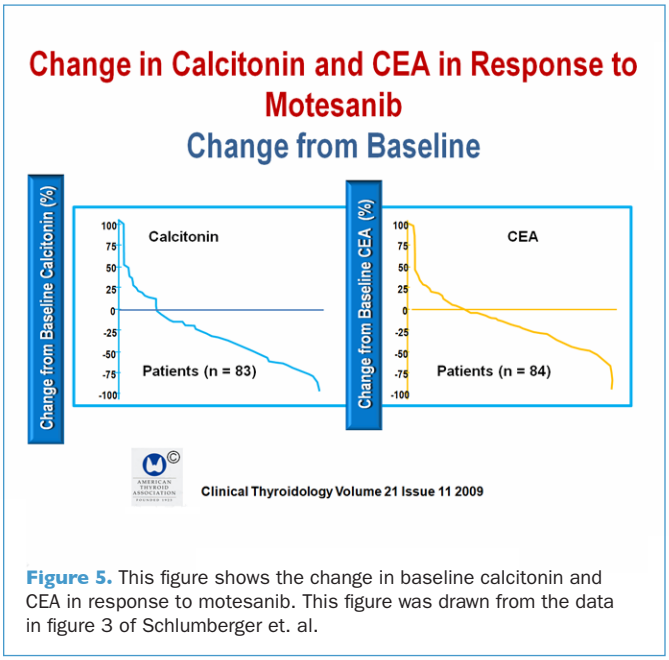

Figure 5. This figure shows the change in baseline calcitonin and CEA in response to motesanib. This figure was drawn from the data in figure 3 of Schlumberger et. al.

The mean (±SD) maximum motesanib plasma concentration of 589±314 ng/ml, was reached in a median of 0.73 hours (range 0.25 to 2 hours), and the mean plasma concentration of the drug 24 hours after the first dose was 7.86 ± 6.58 ng/ml. The mean maximum plasma concentration and area under the curve values were significantly lower than those observed in patients with differentiated thyroid cancer (DTC). Likewise, median trough concentrations were also lower as compared with patients with DTC on the same dosing schedule.

Serum tumor markers (Figure5)
Among the patients with tumor marker analyses, the baseline plasma calcitonin concentrations decreased from baseline in 69 of 83 patients (83%). There also was a decrease in the serum CEA concentration during the study in 63 0f 84 patients (75%). (Fig 3) At some point during the study, calcitonin and CEA levels were ≥50% lower than baseline in 37% and 17% of patients, respectively. A sustained decrease (≥24 weeks) in calcitonin and CEA ≥ 50% as compared with baseline was observed in 2% and 1% of patients, respectively.

CONCLUSION Motesanib achieved low partial response rates; however, the majority of patients (81%) had stable disease. In addition, the medication was well-tolerated.

COMMENTARY

The treatment paradigm for MTC is shifting. Previously, patients with advanced progressive disease were relegated to receiving traditional parenteral chemotherapies which are notorious for their toxic side-effect profile and low response rates (1). With evolving insight into the pathways that promote tumorigenesis and metastatic spread, and apoptosis inhibition, multiple new agents have been created to target refractory thyroid cancers (2). These targeted molecular therapies were initially received with much enthusiasm with the hope that one may offer a cure for MTC. While there have been no complete responses seen with the various agents tested, not all optimism is lost. Vandetanib, an inhibitor of VEGFR 1-3, RET, and EGFR, showed promise for patients with MTC with a partial response rate of 20% and a 30% rate of stable disease (3). Likewise, 87% of patients treated with sorafenib, a multikinase inhibitor with activity against VEGFR 1-3, PDGFR, RET, and BRAF, achieved stable disease as reported in a recent phase II trial (4). These findings, coupled with the high rate of stable disease in this trial by Schlumberger, et al, are encouraging in that VEGFR inhibitors appear to be effective cytostatic agents for patients with progressive MTC.

Because disease stabilization is considered an acceptable endpoint in patients with thyroid cancer, the current methodology of determining objective responses in clinical trials may not be ideal. Further, the existing RECIST criteria do not consider some clinically meaningful endpoints that translate into reductions in tumor burden. For example, patients with bone metastases or bilateral subcentimeter pulmonary metastases are deemed to have non-measurable lesions by RECIST, and a significant proportion of thyroid cancer patients may fall into this category. Reductions in the size of such tumors will not be represented with the existing RECIST criteria. In the study by Schlumberger et al, 76% of patients had significant reductions in tumor burden but were categorized as stable disease by RECIST. Other indications of improving clinical course include tumor markers and symptom control; RECIST does not capture these clinical parameters.

Another important consideration when analyzing the results of the motesanib trial is the pharmacokinetics data. Plasma concentrations of motesanib were consistently lower in the MTC patients than their DTC counterparts on a parallel study (5). It is not known whether the higher objective response rate (14%) in patients with differentiated tumors is attributable to this discrepancy in serum concentrations. The authors have speculated that the higher incidence of diarrhea in MTC patients at study entry may be responsible for a reduction in the absorbed dose of motesanib. It would certainly be valuable to know whether higher doses of motesanib would result in improved response rates; additional studies may be warranted.

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References

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