Motesanib diphosphate can induce partial remissions in patients with progressive advanced metastatic differentiated thyroid cancer unresponsive to surgery, external beam radiotherapy and ^{131}I

Sherman SI, Wirth LJ, Droz JP, Hofmann M, Bastholt L, Martins RG, Licitra L, Eschenberg MJ, Sun YN, Juan T, Stepan DE, Schlumberger MJ. Motesanib diphosphate in progressive differentiated thyroid cancer. N Engl J Med 2008;359:31-42.

SUMMARY

BACKGROUND Thyroid cancers are highly vascular, overexpressing vascular endothelial growth factor (VEGF), which is a potent angiogenesis stimulator associated with aggressive tumor behavior and a poor clinical outcome. Inhibition of VEGF receptor (VEGFR) signaling inhibits the growth of thyroid tumors. This is a study of motesanib diphosphate, an oral, small-molecule tyrosine kinase inhibitor of VEGFR-1, 2, and 3; platelet-derived growth-factor receptor, and KIT in the management of differentiated thyroid cancer (DTC).

METHODS This is an open-label single-group, phase 2 study of motesanib diphosphate in the management of thyroid cancer. Study subjects were patients with progressive, ^{131}I-resistant, metastatic or locally advanced DTC that was not amenable to conventional therapy, who within 6 months before entry into the study, had at least one tumor defined as measurable according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. None had untreated brain metastases and all had disease progression of at least one tumor according to the RECIST criteria. The primary end point of the study was an objective response to 125 mg of motesanib diphosphate administered orally once daily. Secondary end points were the duration of the response, progression-free survival, and changes in serum thyroglobulin (Tg) concentrations, although a rising serum thyroglobulin level was insufficient evidence for disease progression.

RESULTS Study subjects were 93 patients (44 female [47%] and 49 male [53%]) with a median age of 62 years (range, 36 to 81). All had thyroidectomy and external-beam radiotherapy, and 90 (97%) had one or more courses of ^{131}I therapy prior to enrolling in the study. In all, 57 patients (61%) had papillary thyroid cancer, 17 (18%) had Hürthle-cell cancer, 15 (16%) had follicular cancer, and 4 (4%) had other forms of DTC. Tumor was locally advanced in 1 patient (1%) and metastatic in 92 others (99%). All patients received one or more doses of the drug, and 32 (34%) completed 48 weeks of treatment. The other 61 patients discontinued the drug prematurely because of disease progression (35), adverse events (12), patient request (6), or death (5), and 1 each because of withdrawal of consent, an administrative decision, or protocol deviation. The median duration of treatment of all patients was 35 weeks (range, 0.4 to 56), and the median follow-up was 50 weeks (range, 1 to 77). The median time to response was 15 weeks (95% confidence interval [CI], 8 to 27). For all patients, the median duration of progressive-free survival was 32 weeks for a response and 40 weeks for progression-free survival.

Thirteen patients (14%) achieved the primary end point of a confirmed objective response (14%; 95% CI, 7.7 to 22.7), all of which were partial responses (Figure 1). In all, 62 patients (67%) had durable stable disease (24 weeks or more) and 9 others (10%) had unconfirmed partial responses classified as stable disease (Figure 1). In all, 49% of the patients had either durable stable disease or a confirmed partial response, and 7 patients (8%) had disease progression as the best response (Figure 1).Tumor measurements decreased in 69 patients (74%). Median progression-free survival was 40 weeks (95 % CI, 32 to 50; Figure 2). The survival rate at 12 months was 73% (95 % CI, 63 to 83).

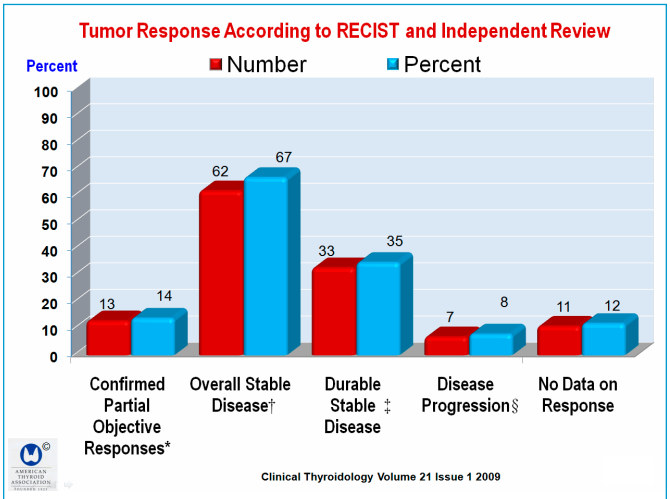

Figure 1. *All confirmed responses were partial. †Nine (10%) unconfirmed responses were classified as stable disease. ‡Durable stable disease is 24 weeks or more. §The best observed response in seven patients (8%). This figure is derived from data in Table 2 in Sherman et al.

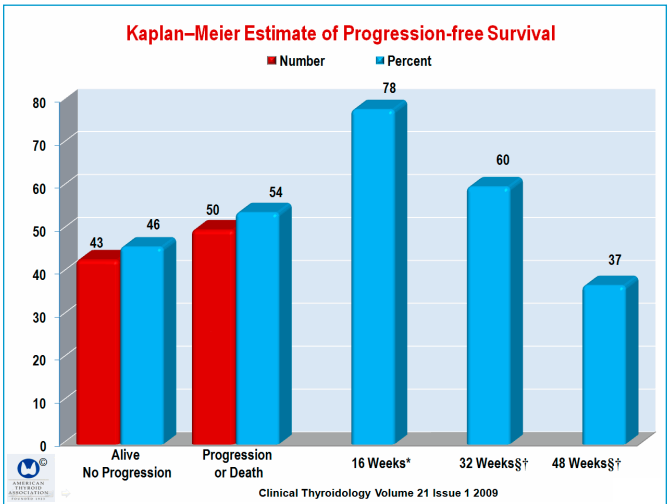

Figure 2. §The Kaplan–Meier estimate of the median duration of progression-free survival was 32 weeks. *Kaplan-Meier progression-free survival at three time periods are shown as percent and †95% Confidence Intervals: 78% (95% CI 69 to 87) 60 (95% CI 50 to 71 and 37 (95% CI 24 to 50) for 16, 32 and 48 wks, respectively. Figure is derived from data in Table 2 in Sherman et al.

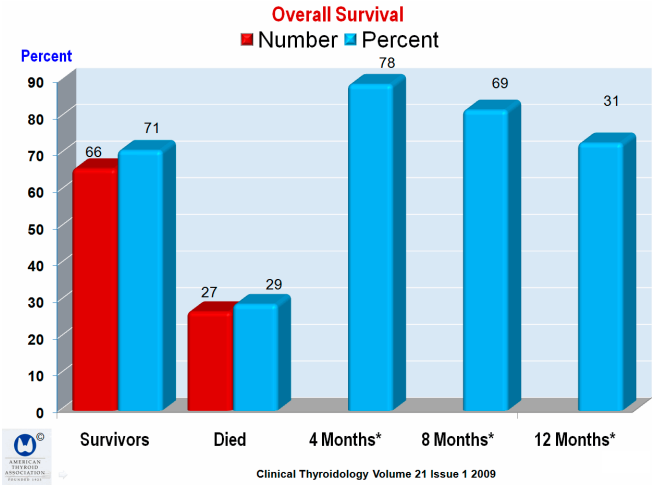

Figure 3. Overall Survival. *Kaplan-Meier estimate of survival at three time periods. This figure is derived from data in Table 2 in Sherman et al.

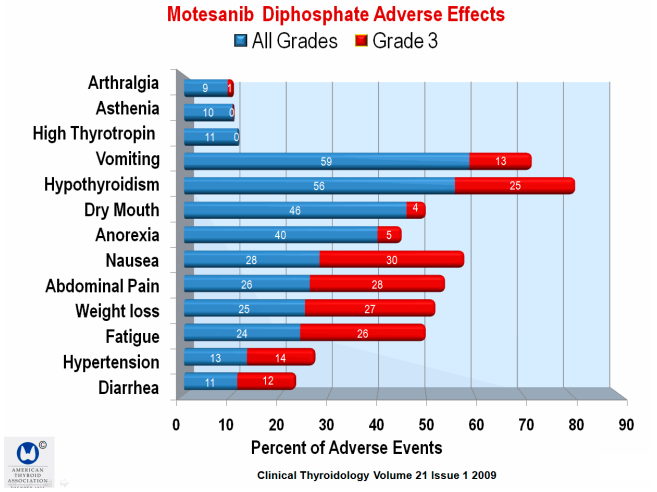

Figure 4. A total of 87 patients (94%) had at least one treatment-related adverse event. The most common treatment-related adverse events were diarrhea in 59% of the patients, hypertension in 56%, fatigue in 46%, and weight loss in 40%. This figure is derived from data in Table 2 in Sherman et al.

Overall, 46 (49%) of the patients had either a confirmed partial response or durable stable disease (Figure 1) and 27 (29%) died of disease (Figure 3).

A total of 87 patients (94%) had at least one treatment-related adverse event, and 2 patients died of disease (Figure 4). In all, 62 patients (67%) had stable disease. Among the 75 patients in whom thyroglobulin (Tg) analysis was performed, 81% had decreased serum Tg concentrations during treatment, as compared with baseline levels.

CONCLUSION Motesanib diphosphate can induce partial responses in patients with progressive advanced ^{131}I-nonresponsive metastatic DTC.

COMMENTARY

Until recently there has been little interest in the development of new drugs for the treatment of thyroid cancer, largely because the vast majority of patients (approximately 80%) have papillary thyroid cancer associated with about a 7% 10-year cancer-specific mortality rate (1). Although cancer death rates are higher in other forms of DTC, most follicular cell tumors can be effectively treated with total thyroidectomy and ^{131}I. As a consequence, even patients with distant or locoregional metastases may have a good prognosis. Yet when deaths do occur, they are caused by metastases that fail to take up enough ^{131}I to make treatment effective, which occurs in up to 75% of the patients, especially older patients and those with tumors that have BRAF mutations. The mainstay of therapy for this advanced stage is usually surgery, external-beam radiotherapy and tumor embolization. When this becomes ineffective, chemotherapy until now has had little impact on outcome, often leaving oncologists and endocrinologists less than enthusiastic about this option for progressive disease. However, the treatment of refractory thyroid cancer is likely to change dramatically in the next year or two. A thoughtful editorial by Pfister and Fagin (2) earlier this year predicted that translation of the advances in our understanding of tumor biology and drug development for thyroid cancer will lead to a paradigm shift in treatment that is likely to benefit patients who until recently have had few therapeutic options. This prediction is already coming true.

This important study by Sherman et al. shows that motesanib diphosphate can induce objective responses among patients with refractory thyroid cancer. The study underscores why oncologists must become involved in the treatment of these patients and why endocrinologists must become familiar with the new drugs that are becoming available, which may have serious adverse effects. This has important implications for the patient concerning day-to-day management. Who is best suited for such treatment? It is likely that the best approach is for both groups of physicians to forge close liaisons, bringing to bear the best expertise of two specialties. Among the myriad management issues, perhaps the most complex is the slow growth of some thyroid cancers, which makes it difficult to know exactly when to treat patients with a new drug. Endocrinologists who have cared for patients over an extended time generally have a good feel for the progression of tumor in their patients. Sherman et al. used a model that practitioners might follow, using the explicit and reproducible RECIST criteria to know when patients should be considered for clinical trials or placed on new drugs known to be effective.

In this issue of Clinical Thyroidology, Dr. R. Michael Tuttle, an expert in the management of advanced thyroid cancer, reviews the changing paradigms that are developing as a consequence of the availability of new thyroid cancer drugs.

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References

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2. Pfister DG, Fagin JA. Refractory thyroid cancer: a paradigm shift in treatment is not far off. J Clin Oncol 2008;26:4701-4.