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An Important Therapeutic Advance for Locally Advanced/ Metastatic Medullary Thyroid Carcinoma: The ZETA Trial

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Despite advances in thyroid cancer treatment, neither chemotherapy nor radiation therapy has been able to improve outcomes for patients with locally advanced or metastatic medullary thyroid carcinoma (MTC). Although MTC accounts for less than 5% of all thyroid cancers, the 10-year overall survival rate in patients with locally advanced or metastatic disease is 40% or less. An international phase III randomized controlled trial involving substantial numbers of patients with MTC, almost all of whom had metastatic disease on study entry, showed that an oral tyrosine kinase inhibitor of multiple signalling pathways significantly prolonged progression-free survival compared with placebo and was reasonably well tolerated. This is the first large-scale demonstration of an agent that can improve outcomes of patients with locally advanced or metastatic MTC and as such, can be regarded as an important therapeutic advance.

Chief Medical Editor: Dr. Léna Coïc, Montréal, Quebec

Findings from the international randomized controlled trial in patients with advanced medullary thyroid cancer (MTC), the ZETA (Zactima Efficacy in Thyroid Cancer Assessment) trial, were recently published in the *Journal of Clinical Oncology*. Significantly prolonged progression-free survival (PFS) was observed for patients with locally advanced or metastatic MTC receiving vandetanib, a once-daily oral tyrosine kinase inhibitor of multiple signalling pathways, compared with placebo, at a predicted median of 30.5 months vs. 19.3 months for placebo.

Pathophysiology

Most thyroid cancers arise from thyroid follicular cells. MTC is a tumour of the calcitonin-producing parafollicular or C cells of the thyroid and accounts for approximately 5% of all thyroid cancers. Seventy-five per cent of MTC presents sporadically, the remainder presents in a heredity pattern. In unselected patients with MTC, the 10-year overall survival (OS) rate is approximately 75% but this drops to about 40% in patients with locally advanced or metastatic disease. No durable objective responses have ever been achieved with either radiotherapy or chemotherapy in patients with advanced MTC.

As discussed by Dr. Samuel Wells, Jr., Senior Clinical Scientist and Director of the Thyroid Oncology Clinic, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, and multicentre colleagues, virtually all patients with hereditary MTC have germline mutations in the RET proto-oncogene, whereas approximately half of patients with sporadic MTC have somatic RET mutations and 85% of them have the M918T mutation. "Other signalling pathways likely to contribute to the growth and invasiveness of MTC include vascular endothelial growth factor receptor (VEGFR)-dependent tumour angiogenesis and epidermal growth factor receptor (EGFR)-dependent tumour cell proliferation," investigators added. Vandetanib selectively targets RET, VEGFR and EGFR signalling.

ZETA Trial Results

In an international randomized, placebo-controlled, double-blind phase III study, Dr. Wells and colleagues randomized 331 patients to either vandetanib at a starting dose of 300 mg/day or placebo; patients were treated until disease progression. "The primary objective was to determine whether vandetanib, compared with placebo, prolonged PFS on the basis of independent central review," the authors stated. Secondary assessments included objective response rate, disease control rate at 24 weeks, duration of response, OS, time to worsening of pain and biochemical response to treatment. Ninety per cent of the cohort had sporadic MTC and 95% had metastatic disease on study entry.

At a median follow-up of 24 months, "37% of patients had progressed and 15% had died," investigators reported. However, PFS was 54% longer (HR 0.46) or an estimated 11 months in patients receiving vandetanib compared with placebo ($P<0.001$). At 6 months, 83% of patients receiving active therapy were alive and free of disease progression vs. 63% of placebo controls. Benefit in PFS rates was observed in patients with both the hereditary and the sporadic forms of MTC.

Patients randomized to the targeted therapy arm also had higher objective response rates compared with placebo (45% vs. 13%), disease control rates (87% vs. 71%), calcitonin biochemical response rates (69% vs. 3%) and carcinoembryonic antigen (CEA) biochemical response rates (52% vs. 2%). "Objective responses were durable on the basis of the median duration of response not being reached at 24 months of follow-up," investigators added. Regarding disease progression, patients could elect to enter open-label treatment with vandetanib until a withdrawal criterion was met. As investigators pointed out, 12 of 13 responses observed in patients initially assigned to placebo occurred while they were receiving vandetanib in the open-label phase.

Overall survival data were immature at data cutoff but a final survival analysis will take place when half of the cohort has died.

Continued

Safety and Tolerability

During the randomized phase of the study, median duration of treatment was 90.1 weeks for those assigned to the active treatment arm and 39 weeks for placebo patients. The incidence of grade 3 and higher adverse events (AEs) for the active treatment vs. placebo were: diarrhea, 11% vs. 2%; hypertension, 9% vs. 0%; prolonged QT interval, 8% vs. 1%; fatigue, 6% vs. 1%; and decreased appetite/rash, 4% vs. 0 and 1%, respectively.

"More patients required dose reduction of vandetanib compared with placebo for AEs or QTc prolongation (35% vs. 3%)," the authors observed, but there were no reports of torsades de pointes. Almost half of patients on vandetanib on study entry also required an increase in thyroid replacement vs. fewer than 20% of their placebo counterparts. The authors also pointed out that the majority of AEs were manageable according to standard clinical practice, alone or in combination with dose reductions, which allowed patients to continue on treatment for an extended period of time.

Another Oral Agent

As reported by Kurzrock et al. in an earlier issue (*J Clin Oncol* 2011;29:2660-6), a phase I dose-escalation study of another oral agent, cabozantinib, was carried out in 85 patients with advanced solid tumours including 37 patients with MTC. The oral agent inhibits MET as well as RET and VEGFR, and preclinical studies have shown it has robust antiangiogenic, antitumour and anti-invasive effects.

Results showed that the maximum tolerated dose was 175 mg q.d., as the authors reported. Dose-limiting toxicities included grade 3 palmar plantar erythrodysesthesia, mucositis and elevated liver enzymes. Ten patients out of 35 with MTC with measureable disease had a confirmed partial response while overall, 18 patients had evidence of tumour shrinkage of 30% or more, including almost half (17 patients of the 35 patients) with MTC with measurable disease. Disease stabilized for at least 6 months in 15 out of 37 patients with MTC, resulting in stable disease for 6 months or longer or confirmed partial response in 68% of patients with MTC.

Editorial Comments

Editorialists Dr. Benjamin Solomon and Dr. Danny Rischin, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia, maintained that the potential toxicity associated with long-term use of the drug highlights the importance of appropriate selection of patients for treatment with this agent. "The risk:benefit ratio of treatment is likely to be unfavourable in asymptomatic patients or patients with a low disease burden who experience slow progression," they stated. For these patients, the authors suggested that they might be appropriately monitored while not receiving therapy. In contrast, symptomatic patients, patients with a high disease burden or patients with rapidly progressing disease stand to benefit from vandetanib treatment.

Questions and Answers

Questions and answers with Dr. Samuel Wells, Jr., Senior Clinical Scientist and Director of the Thyroid Oncology Clinic, National Cancer Institute, Bethesda, Maryland.

Q: How important a therapeutic advance is vandetanib for this patient population?

A: Until now, there has been no treatment for patients with MTC who develop locally advanced or metastatic disease. The majority of patients with MTC have mutations in the RET proto-oncogene. Dr. Massimo Santoro's group in Naples, Italy, found that ZD6474 (vandetanib), an oral inhibitor of KDR tyrosine kinase activity, blocks oncogenic RET kinases, thus setting the stage for the current clinical trial. Now that the Food and Drug Administration has approved vandetanib, it has become the standard of care for this disease. The starting dose for patients is 300 mg orally per day. Generally, the drug is well tolerated.

Q: Which patients with locally advanced or metastatic MTC do you think are good candidates for vandetanib and which ones are not?

A: A fair number of patients with MTC have very indolent disease; it might even be metastatic or locally recurrent. Often the disease progresses slowly and patients are asymptomatic. The majority of these patients can be monitored without treatment for evidence of tumour enlargement or symptoms. The hormone calcitonin is secreted by the MTC cells and is an excellent tumour marker. The rate at which serum calcitonin levels double has prognostic significance. For example, patients whose calcitonin levels double in 6 months or less have a worse prognosis than those whose calcitonin levels double in 12-24 months. Treatment with vandetanib is not based on serum calcitonin levels alone, but if patients have progressive regional or metastatic disease, or are symptomatic, treatment is indicated.

Q: What about prolongation of the QTc interval with vandetanib? Is that of some concern?

A: It is not uncommon to see a delayed QT interval in patients treated with vandetanib. All patients need to be monitored with electrocardiograms while receiving vandetanib, especially early in the course of treatment. In the phase II and III trials with vandetanib this did not prove to be a frequent problem, but because of the seriousness of this side effect, it is important that it be monitored and the drug stopped if certain predetermined criteria are met. □

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