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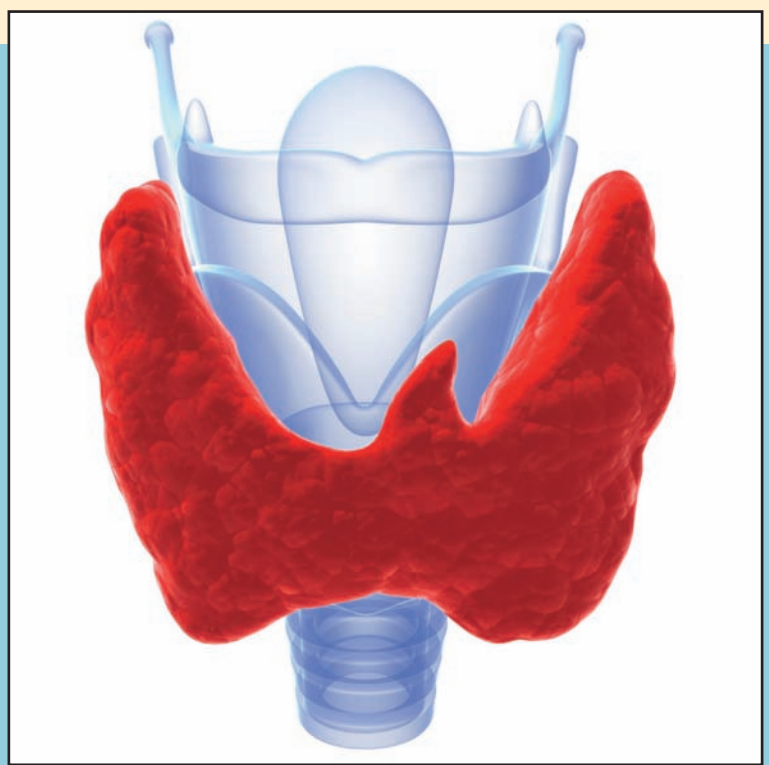

#2 in a Series

FOCUS:

Thyroid Cancer

Treatment & Research Updates

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Pazopanib-Paclitaxel Combination Shows Early Promise Against Anaplastic Thyroid Cancer

BY KURT SAMSON

Researchers at the Mayo Clinic are getting promising early results treating anaplastic thyroid cancer (ATC) patients with a combination of pazopanib and paclitaxel. As reported in *Science Translational Medicine* (***2013;5:166ra3***), the combination killed ATC cells more effectively than either agent did alone, with growth of tumors implanted into mice significantly inhibited.

In addition, a pilot study in one patient with metastatic disease showed tumor shrinkage that lasted for six months. Building upon these data, a clinical trial of the combination, together with radiation therapy, has already been started.

> The mechanisms underlying the synergy between pazopanib and antimicrotubule agents like paclitaxel have raised awareness of the potential significance of aurora A and other cell cycle-critical kinases as candidate therapeutic molecular targets in anaplastic thyroid cancer, where aurora A is significantly overexpressed.

"Without formal statistical analyses that require study completion, the role of the combination in ATC remains incompletely defined," said the senior researcher for the study, Keith C. Bible, MD, PhD, Associate Professor of Pharmacology and Assistant Professor of Medical Oncology. "We are, however, getting some very encouraging initial results, not just in Stages 4A and 4B tumors, but also in metastatic tumors. We are hopeful that this combination may have a real impact on ATC outcomes."

Anaplastic thyroid cancer is very aggressive, and tumors can sometimes double in size in just a few days, he said. "What is especially interesting is that the noted synergy between pazopanib and microtubule inhibitors seems to be very class-specific.

ATC typically occurs in patients in their 60s and 70s and is resistant to most current therapies. Median survival is only about five months after diagnosis, and fewer than one in five patients survives for a year.

Pazopanib is a multi-targeted tyrosine kinase-inhibitor that interferes with cancer cell growth and has been approved by the Food and Drug Administration to treat renal cell carcinoma and soft cell sarcoma. The chemotherapy agent paclitaxel is an FDA-approved mitotic inhibitor that stabilizes microtubules and inhibits cell division, promoting cell death in some tumors.

Bible noted that because monotherapy with pazopanib was found in earlier studies to have disappointing activity against ATC, paclitaxel was added to address the aggressiveness of these tumors and bolster anti-cancer effects.

Interrupting Cell Division

The researchers used time-lapse microscopy to study the combination's effects on ATC cells as they multiplied, and found that the combination resulted in abnormal cell division and an increase in ATC cell death. Until now, pazopanib had not been shown to specifically affect cell division. But based upon early results, the team suspected that it might have another previously unrecognized target within cancer cells.

The mechanisms underlying the synergy between pazopanib and antimicrotubule agents like paclitaxel have raised awareness of the potential significance of aurora A and other cell cycle-critical kinases as candidate therapeutic molecular targets in ATC, where aurora A is significantly overexpressed. The findings suggest that the combination might also be useful in treating other cancers in which aurora A is sometimes found to be present in elevated amounts, as it is in ATC, Bible said.

KEITH C. BIBLE, MD, PHD: "We are getting some very encouraging initial results, not just in Stages 4A and 4B tumors, but also in metastatic tumors. We are hopeful that this combination may have a real impact on ATC outcomes."

"Pazopanib inhibits both aurora A and B, and it is still unclear whether pazopanib/paclitaxel synergy is related to one or the other, although studies suggest that it is more likely inhibition of aurora A. What we do know is that the combination markedly impairs tumor cell division and promotes cell death prior to completion of cell division."

These results may have implications for drug development that go beyond pazopanib, he added. "Additional selective aurora kinase inhibitors and/or inhibitors

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of other cell cycle-critical kinases could represent promising therapeutic approaches for ATC, especially when combined with other antimicrotubule agents."

New Treatment Impasse

Asked for a comment for this article, Francis P. Worden, MD, Associate Professor of Medical Oncology and Director of the Hematology/Oncology Fellowship Program at the University of Michigan Comprehensive Cancer Center, said, "This is a breakthrough for such a devastating disease."

In a 2010 study, he and his colleagues tested imatinib as a targeted treatment in 11 patients with ATC who overexpressed alpha-type platelet-derived growth factor receptor (PDGFR) (***Ha et al: Thyroid 2010;20:975-980***). The treated patients had a six-month progression-free survival rate of 36 percent and six-month overall survival rate of 45 percent.

"Treatment for ATC remains very poor, and the last drug that was approved was in the 1970s," he said.

"I believe that the findings from this study are very promising, especially in light of other research that is being conducted with microtubulin inhibitors, such as crolibulin. Such targeted therapies offer a potential advantage over conventional cytotoxic chemotherapy alone. This study suggests that synergy with pazopanib and paclitaxel may improve the effect of the paclitaxel in patients with ATC, and that aurora A may be a viable therapeutic target.

FRANCIS P. WORDEN, MD: "The findings from this study are very promising, especially in light of other research that is being conducted with microtubulin inhibitors, such as crolibulin. This study suggests that synergy with pazopanib and paclitaxel may improve the effect of the paclitaxel in patients with ATC, and that aurora A may be a viable therapeutic target."

"It is too early to tell if the combination will have any proven benefit overall over single-agent paclitaxel in human subjects," he continued. "It is, however, worth pursuing in the RTOG clinical trial."

The rapid speed of progression of ATC makes research difficult, he noted, but there are a small number of patients whose local disease does respond to radiation. "These patients subsequently develop distant metastases, which are amenable to treatment with chemotherapy.

> "The results may have implications for drug development that go beyond pazopanib: Additional selective aurora kinase inhibitors and/or inhibitors of other cell cycle-critical kinases could represent promising therapeutic approaches for ATC, especially when combined with other antimicrotubule agents."

"In patients treated with single-agent paclitaxel, the response rates are approximately 50 percent, but this unfortunately does not translate to a survival advantage. Our goal with ATC is to ultimately improve survival as well as response."

Human Trial Underway

The researchers, together with investigators at Memorial Sloan-Kettering Cancer Center, are at the starting point of a complex multicenter clinical trial being administered by the National Cancer Institute and the Radiation Therapy Oncology Group. The study will ultimately compare the effects of paclitaxel monotherapy with the pazopanib-paclitaxel doublet as initial therapy in 88 patients with ATC, when administered with intensity-modulated neck radiation therapy.

> "In patients treated with single-agent paclitaxel, the response rates are approximately 50 percent, but this unfortunately does not translate to a survival advantage. Our goal with ATC is to ultimately improve survival as well as response."

Already completed is the first of two run-in phases, Bible said. "An initial problem we have had to address is that pazopanib had previously been available only in tablet form. However many ATC patients have difficulty swallowing, so instead we are now using a recently available pediatric elixir, adjusted for adult dosing.

"There have also been some treatment delays because some subjects had liver test abnormalities, but so far the results, while anecdotal, are very favorable."

He said the researchers anticipate starting the next phase of their study within four to six weeks, and it will likely take four to six months to collect and assess safety data before moving on the randomized efficacy phase.

"To date, trial accrual has been remarkably rapid, and we are hopeful that the trial may be completed as soon as 24 months after initiation of its final phase."