# ‘Soft’ Chemo Plus Targeted Therapy Works in HER2 Breast Cancer

## Action Points

- Note that this randomized trial found that the addition of the somewhat “gentle” chemotherapy metronomic oral cyclophosphamide to pertuzumab and trastuzumab increased progression-free survival among older women with HER-2 positive breast cancer.
- Be aware that these patients were all either over 70 years old, or over 60 with certain functional limitations.

A combination of “soft” chemotherapy and anti-HER2 therapy is effective in older patients with HER2-positive metastatic breast cancer and comes with an acceptable safety profile, investigators have found.

Specifically, they determined that the use of trastuzumab and pertuzumab with the “softer” chemotherapy metronomic oral cyclophosphamide provided patients with seven months longer progression-free survival compared to patients who were treated with trastuzumab and pertuzumab alone.

The study, led by Hans Wildiers, MD, PhD, University Hospitals Leuven, in Belgium, was published in *The Lancet Oncology*.

As pointed out by Wildiers and his colleagues, while HER2-positive metastatic breast cancer is particularly aggressive if left untreated, advances in HER2-directed drug development have resulted in improvements in outcomes.

For example, the phase 3 CLEOPATRA Trial showed that the

addition of trastuzumab to pertuzumab and the chemotherapy drug docetaxel significantly improved progression-free survival, as well as overall survival.

While docetaxel combined with trastuzumab and pertuzumab has been shown to be effective in younger patients with HER2 positive metastatic breast cancer, it can be significantly toxic and affect quality of life, particularly in older patients.

The question Wildiers and his colleagues wanted to address was whether the introduction of HER2–directed therapies makes it possible to treat older HER2-positive metastatic breast cancer patients with HER2-targeted regimens and without classical therapies.

They pointed out that the dual blockade of HER2 with trastuzumab and pertuzumab has shown substantial anti-tumor activity. At the same time metronomic chemotherapy with oral cyclophosphamide has shown antitumor activity with minimal toxicity, making it more suitable for older patients.

“Given the need to develop new treatment strategies with limited toxicity for older patients with breast cancer, we aimed to examine the safety and activity of dual anti-HER2 treatment with or without metronomic chemotherapy in this population,” Wildiers and his colleagues wrote.

In this open-label, randomized, phase II trial, 80 patients were randomly assigned to receive trastuzumab and pertuzumab (TP) or TP plus metronomic oral cyclophosphamide (TPM). The patients were 70 years of age or older, or 60 years or older if they presented with certain functional limitations. The median age of the study participants was 76.7 years.

Wildiers and his colleagues found that estimated progression-free survival at 6 months was 46.2% (95% CI, 30.2-60.7) with TP alone compared to 73.4% (95% CI, 56.6-84.6) with TPM. At a median follow-up of 20.7 months, the median progression-free

survival was 5.6 months (95% CI, 3.6-16.8) in the TP group versus 12.7 months (95% CI, 6.7-24.8) in the TPM group.

The most frequent grade 3-4 adverse events included hypertension (in 6 [15%] of 39 patients in the trastuzumab and pertuzumab group versus 5 [12%] of 41 in the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group), diarrhea (4 [10%] versus 5 [12%]), dyspnea (2 [5%] versus 4 [10%]), fatigue (3 [8%] versus 2 [5%]), pain (2 [5%] versus 2 [5%]), and a thromboembolic event (0 [0%] versus 4 [10%]).

In a press release Wildiers called the results "encouraging," since he and his colleagues were able to show that the use of gentle therapy among older, frail patients could delay tumor growth while delaying or even avoiding the use of more toxic chemotherapy.

"In this age group, maintenance of [quality of life] and the avoidance of toxic side-effects may be just as important as survival," he said.

"We believe that there is a strong case for carrying out trials designed specifically for older people," Wildiers added. "However, financial support for such trials is very difficult to find. Additionally, older patients are far less likely to receive standard chemotherapy, and are also unlikely to be included in a randomized trial where there is a risk that they will receive a treatment with high toxicity."

In a commentary accompanying the study, Charles E. Geyer, MD, Massey Cancer Center, Virginia Commonwealth University, also noted that while clinical trials are a prerequisite for establishing new treatment standards, "eligibility criteria generally restrict participation to fit populations with minimal comorbidities," which, in turn, results in the underrepresentation in clinical trials of older patients with functional limitations.

Thus, Wildiers and his colleagues "are to be congratulated on

their demonstration of a framework for clinical trials in older, more frail patients with HER-positive-metastatic breast cancer," wrote Geyer.

Wildiers reports research grants from Roche and personal fees towards his institute from Roche, Amgen, Novartis, Pfizer, Puma, and Celldex. Geyer has received personal fees from Myriad and Heron Therapeutics for advisory board participation and travel support from AstraZeneca, Genentech, and Macrogenics, outside the submitted work.

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