

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Lapatinib Plus Capecitabine in Patients With HER2-positive Advanced Breast Cancer

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H&O Could you discuss the prior research that led to the phase III trial of lapatinib plus capecitabine in women with HER2-positive advanced breast cancer?

DC Lapatinib (Tykerb, GlaxoSmithKline) is a small-molecule tyrosine kinase inhibitor that binds to HER2 receptors, blocks receptor activation, and inhibits downstream signaling cascades. Its activity was discovered in multiple cell lines, and it was found, based on phase II trials, to be active in patients with HER2-positive breast cancer that had progressed after treatment with trastuzumab (Herceptin, Genentech). Based on this research, it was concluded that a phase III trial of lapatinib in patients who had previously received therapy with an anthracycline, a taxane, and trastuzumab was indicated. Because no single standard combination regimen including lapatinib had been developed, researchers needed to determine which agent to combine with lapatinib in the setting of the phase III trial. Capecitabine (Xeloda, Roche) was felt to be the logical choice as a chemotherapeutic agent, and the phase III trial was designed wherein patients were randomized to either capecitabine plus lapatinib or capecitabine alone. All patients had locally advanced or metastatic disease that had progressed after previously receiving anthracyclines, taxanes, and trastuzumab. No specific anti-HER2 agents were known to be effective in this setting, and the patients clearly needed another treatment option.

H&O What were the main findings of this trial?

DC Three hundred and ninety-nine patients were enrolled in this trial. Their median age was 53 years, and 14% were older than 65 years. Lapatinib was administered at a dose of 1250 mg per day continuously plus capecitabine at a dose of 2000 mg/m² on days 1–14 of a 21-day cycle, and capecitabine monotherapy was administered at a dose of 2500 mg/m² on days 1–14 of a 21-day cycle. The main finding of the trial was that the addition of lapatinib to capecitabine doubles the time to progression. In this case, improvement in the median time to progression of between 3 and 4 months was observed. Moreover, not only was there a median improvement, but an improvement in time to progression was observed in all patients who received the combination. The hazard ratio for the time to progression was 0.49 (95% confidence interval, 0.34–0.71; $P < 0.001$; Table 1), with 49 events in the combination-therapy group and 72 events in the monotherapy group. The median time to progression was 8.4 months in the combination-therapy group and 4.4 months in the monotherapy group. An increase in response rate was observed, but the primary endpoint was time to progression, which was found to be statistically and clinically significant. This improvement was achieved without any increase in serious toxicity. There was some increase in low-grade diarrhea and a small increase in skin disorders associated with the combination. As an anti-HER2 agent, there was concern as to whether lapatinib

Table 1. Lapatinib Plus Capecitabine Versus Capecitabine Alone: Efficacy Endpoints in the Intention-to-Treat Population

Endpoint	Lapatinib plus Capecitabine (n=163)	Capecitabine Alone (n=161)	Hazard Ratio (95% CI)	P Value
Median time to progression, mo	8.4	4.4	0.49 (0.34–0.71)	<.001*
Median progression-free survival, mo	8.4	4.1	0.47 (0.33–0.67)	<.001*
Overall response, % (95% CI)	22 (16–29)	14 (9–21)		.09†
Complete responders (%)	1 (<1)	0 (0)		
Partial responders (%)	35 (21)	23 (14)		
Patient experiences clinical benefit (%)	44 (27)	29 (18)		
Deaths (%)	36 (22)	35 (22)		

CI=confidence interval.

*Calculated using the log-rank test.

†Calculated using Fisher's exact test.

Data taken from Geyer CE, et al. *N Engl J Med.* 2006;355:2733-2743.

would show cardiac toxicity; a few cases of a decrease in ejection fraction were observed, but all patients recovered. Overall, no significant cardiac toxicity was observed. Thus, the results can be summarized as a doubling of time to progression with only a mild increase in toxicity. As such, it is hoped that this combination therapy will become one of the standards of care in this setting.

H&O What contraindications exist for the combination of capecitabine and lapatinib?

DC The protocol for this trial defined a number of exclusion criteria. For example, there are patients for whom capecitabine is not appropriate. Those patients with severely damaged renal function should not receive capecitabine, as it is excreted renally. Capecitabine is converted into 5-fluorouracil (5-FU), which some patients cannot tolerate due to a rare syndrome of a deficiency of the requisite clearance enzyme. Additionally, some patients develop cardiac problems when they receive 5-FU and thus should not receive capecitabine. If capecitabine is contraindicated, the combination is therefore contraindicated. From the perspective of lapatinib in the combination, there are some further concerns. The metabolism of lapatinib is affected by several other drugs; thus, in the protocol, concomitant CYP3A4 inhibitors were not allowed. It is important to note that no patients with pre-existing cardiac damage were allowed to enroll in the trial. Therefore, we do not know the safety signal for patients who do already have cardiac damage. Trastuzumab cannot

be administered to patients with preexisting cardiac damage, and, although the effects of lapatinib in patients with such preexisting damage are unknown, it is appropriate to exercise caution with such patients.

H&O Are there any data comparing combinations of capecitabine and trastuzumab or capecitabine plus lapatinib either to capecitabine alone or to each other in the setting of HER2-positive patients with advanced breast cancer?

DC The simple answer is not yet. There are no good data on capecitabine plus trastuzumab versus trastuzumab alone. A German group is accruing patients presently for such a study. In our trial, all patients had previously received trastuzumab, so it remains worthwhile to study the efficacy of lapatinib versus trastuzumab in patients who have not received trastuzumab. No head-to-head comparative data exist now, but trials are currently ongoing to address this comparison in patients with advanced breast cancer, as well as in patients at an earlier stage of disease. A comparison of lapatinib to trastuzumab in patients who have already received trastuzumab and whose cancer has progressed is possible, though it is hypothesized that the efficacy of trastuzumab re-treatment would be limited because the cancer has already grown despite prior administration of the agent. Nevertheless, it has not been proven that lapatinib would be more effective than trastuzumab in patients who have already received trastuzumab.

H&O Has lapatinib been studied in patients who are not HER2-positive?

DC The combination of lapatinib and capecitabine was found to be effective in the trial only in HER2-positive patients. HER2-negative patients would not receive trastuzumab, so no HER2-negative patients were included. There are other trials that are looking at the possible activity of lapatinib irrespective of HER2 status, but this trial gives us no data in that regard. Indeed these other trials have not yet reported any data. It is known that capecitabine is active in HER2-negative patients, but it is not known whether the addition of lapatinib to capecitabine in HER2-negative patients would confer additional benefit. That question remains unanswered presently, but studies should begin to answer it in the future.

H&O How do the findings of this trial lead to further research with other agents?

DC Some other settings that deserve research based on these findings are lapatinib in combination with agents besides capecitabine as well as lapatinib and capecitabine

given earlier in the disease course, in the adjuvant setting, and prior to trastuzumab. Additionally, as a result of these findings, there is interest in researching other tyrosine kinase inhibitors in the setting of HER2-positive advanced breast cancer. None of the other anti-HER2 agents are as developed as lapatinib, with the possible exception of the monoclonal antibody pertuzumab (Genentech). A legitimate question is whether any of these other agents have the same activity as lapatinib in the same setting. More research is needed to compare lapatinib with up-and-coming competitors, but such trials have not yet been initiated.

Suggested Readings

- Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med.* 2006;355:2733-2743.
- Di Leo A. The state of HER-2 status. *Ann Oncol.* 2007;18:813-815.
- Ito Y, Tokudome N, Sugihara T, Takahashi S, Hatake K. Does lapatinib, a small-molecule tyrosine kinase inhibitor, constitute a breakthrough in the treatment of breast cancer? *Breast Cancer.* 2007;14:156-162.
- Tripathy D. Capecitabine in combination with novel targeted agents in the management of metastatic breast cancer: underlying rationale and results of clinical trials. *Oncologist.* 2007;12:375-389.