Evaluation of lapatinib as a component of neoadjuvant therapy for HER2+ operable breast cancer: NSABP protocol B-41

Presenter: Andre Robidoux
Affiliation: National Surgical Adjuvant Breast and Bowel Project and Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada

Background

- Trastuzumab (Herceptin) is a monoclonal antibody directed against HER-2, or the Human Epidermal Growth Factor Receptor 2. Over-expression of HER-2 has been shown to correlate with the pathogenesis and progression of certain types of malignant breast cancer, and has become an important target of therapy.
- Since the publication of the NSABP B31 trial in 2005, which demonstrated improved disease free survival and lower risk of death with trastuzumab, the drug has become a standard part of the treatment paradigm for HER2-overexpressing breast cancers.
- The success of trastuzumab, however, has been tempered by the development of resistance by various mechanisms, late cardiac toxicity, and a concerning pattern of CNS relapse associated with the drug.
- Lapatinib is a dual tyrosine kinase receptor inhibitor against both HER2 and EGFR. Promising in vitro studies and phase II/III clinical data suggest that lapatinib may benefit patients with trastuzumab-resistant tumors, decrease CNS relapses, and have significantly lowered risk of cardiac toxicity.
- There is also a possiblity of synergy between trastuzumab and lapatinib, as the two drugs have different mechanisms of action.
- The current standard of care for neoadjuvant chemotherapy for HER2-overexpressing breast cancers is doxorubicin and cyclophosphamide followed by weekly paclitaxel and trastuzumab.
- Lapatinib is currently approved for use with capecitabine for advanced or metastatic breast cancer in patients with HER2-overpression.
- The objective of the NSABP B41 trial was to
- Determine the effect of substituting lapatinib (L) for trastuzumab (T) in combination with weekly paclitaxel (WP) following doxorubicin and cyclophosphamide (AC)
- Determine the effect of adding L to T with WP following AC

Methods

- 529 patients were accrued over 47 months from July 2007 to June 2011.
- Study entry criteria included women with a palpable tumor > 2 cm diagnosed by core needle biopsy, with HER2 gene amplification detected with FISH or positive IHC. Women were required to have left ventricular ejection fraction of 50% or greater.
- Women with HER2-positive operable breast cancer received standard AC q 3wks x 4 cycles followed by WP (80 mg/m2) on days 1, 8, and 15 q28 days x 4 cycles.
- Concurrently with WP, patients received either T (4 mg/kg load, then 2 mg/kg) weekly until surgery, L (1250 mg) daily until surgery, or weekly T plus L (750 mg) daily until surgery.
- Following surgery, patients received trastuzumab to complete 52 wks of HER2-targeted therapy.
- The primary endpoint of the study was pathologic complete response (pCR) in the breast.
- pCR was defined as the absence of invasive tumor in the resected breast specimen and nodes

- Secondary endpoints included cardiac toxicity, non-cardiac toxicity, and clinical complete response (cCR). Recurrence-free survival and overall survival were not discussed in this presentation.
- The study was designed with 90% power to detect superiority of the lapatinib arms assuming a pcR in breast of 42% with trastuzimab arms.
- For each of the two primary comparisons, the Fisher's exact test was used to test the equality of pCR rates.

Results

- Of the 529 patients enrolled, 85% were white, 57% had tumor > 4 cm, 51% were clinically node positive and 63% had hormone receptor positive (HR+) tumors. Treatment arms were well balanced in baseline characteristics.
- pCR assessments were available from 519 of 529 patients.

	ACàWP + T (%)	**ACàWP + L (%)**	**ACàWP + T + L (%)**	**p-value, T vs. L**	**p-value, T vs. T + L**
Outcomes					
pCR	52.5	53.2	62	0.990	0.095
pCR for HR+ subset	46.7	48	55.6	0.850	0.180
pCR for HR- subset	65.5	60.6	73	0.570	0.370
pCR breast and nodes	49.4	47.4	60.2	0.780	0.056
cCR	82	69.9	76.8	**0.014**	0.300
pCR low IHC, + FISH	*41.7*	*60.9*	*25*	*0.310*	*0.330*
pCR high IHC, + FISH	*54.7*	*53.2*	*71*	*0.89*	**0.006**
Toxicity					
Grade 3 or 4 diarrhea	2	20	27	<0.001	< 0.001
Grade 3 or 4 left ventricular systolic dysfunction	4	4	2	0.490	
Febrile neutropenia	4	2	5	0.530	
Rise in ALT (liver enzymes), Grade 3	2	1	2	0.370	
Treatment					
Completion of therapy	78	68	63	**0.010**	

- Following neoadjuvant chemotherapy, 50% of women had breast conservation surgery and 50% had mastectomy.

Axilllary nodal staging was performed for 97-98% of women after neoadjuvant chemotherapy was completed.

- An unplanned exploratory analysis was performed to evaluate the importance of IHC level when FISH was positive for HER2 overexpression. 112 patients with positive FISH had IHC levels reviewed in a central lab. Results of pCR analysis are included in table above.

Author's Conclusions

- Substitution of lapatinib for trastuzumab in combination with the chemotherapy program employed in this study resulted in similar high percentages of pCR in both HR+ and HR- cohorts.
- Combined HER2-targeted therapy produced a numerically higher pCR percentage than single agent HER2-directed therapy, but the difference was not statistically significant.
- A higher proportion of patients discontinued therapy in the combination arm, and grade 3 diarrhea was the main toxicity noted.
- Central review of HER2 and ER is being conducted to determine if subsets benefiting from the combined HER2-targeted therapy can be identified.
- Combined HER2-targeted therapy may be of greatest benefit to patients with high levels of IHC expression

Scientific/Clinical Implications

- This very important study investigated the substitution of lapatinib for trastuzumab, as well as the use of combined HER2 targeted therapy, in the neoadjuvant setting.
- Findings suggested that although there may be a benefit to combined therapy in patients with high IHC levels, there were no other significant pCR benefits noted with substitution of lapatinib or combined therapy with lapatinib and trastuzamab.
- Furthermore, significantly higher rates of grade 3 and 4 diarrhea were noted with the use of lapitinib, and rates of cardiac toxicity were comparable between to the two treatment regimens. Rates of CNS relapse were not assessed in this study.
- This study must be interpreted in the context of other similar trials investigating the use of lapitinib as part of a neoadjuvant regimen
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    - The Neo-AItto Phase III study (Baselga, Lancet 2012) showed a more prominent pCR benefit for combined lapatinib and trastuzumab after chemotherapy (pCR 51.3%) as compared with trastuzumab alone after chemotherapy (pCR 29.5%). Patients in this study received 18 weeks of HER2 targeted therapy. Interestingly, the pCR rates for the control arm in the NSABP B41 study were much higher than the control arm in the Neo-AItto study. Grade 3 diarrhea and liver enzyme alterations in the Neo-AItto study were more common with lapitinib arms.
    - The GeparQuinto Phase III study (Untch, Lancet Oncology 2012) compared traztuzumab alone after chemotherapy to combined HER2 targeted therapy with trastuzumab and lapatinib after chemotherapy. Patients in this study received a total of 24 weeks of HER2 targeted therapy. GeparQuinto showed a higher pCR rate for trastuzumab alone after chemo (pCR 30.3%) as compared to combination therapy (22.7%).
- These three studies comparing trastuzumab and lapitinib after chemotherapy highlight the challenges that exist in interpreting these data. The type of chemotherapy, duration of HER2 targeted therapy, and definition of pCR varied among the three studies, and therefore useful comparisons are difficult to make.
- Nonetheless, the unique contribution of the NSABP B41 study is the identification of a subgroup of patients with high IHC levels that may derive benefit from combined HER2 targeted therapy.