Preoperative Chemotherapy plus Lapatinib or Trastuzumab or Both in HER2-Positive Operable Breast Cancer (CHERLOB Trial)

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Rationale

Primary systemic therapy is the standard of care for locally advanced and inflammatory breast carcinoma, and is progressively more applied also in earlier stages of disease. Nowadays, this strategy can be considered a reasonable alternative to postoperative therapy for all patients who are candidates for adjuvant chemotherapy.

In patients with HER2-positive tumors, several trials evaluating adjuvant trastuzumab have shown a clear advantage compared with chemotherapy alone.1-4 Therefore, trastuzumab represents an essential component of the adjuvant treatment of HER2-positive breast cancer.

In the preoperative setting, the combination of trastuzumab to sequential chemotherapy with taxanes and anthracyclines resulted in an impressive rate of pathologic complete responses (pCRs),5 which represents a powerful marker of long-term outcome6,7. However, not all the patients equally benefit from trastuzumab therapy, and many different intracellular pathways can contribute to the intrinsic or acquired resistance to HER2 blockade.8 Lapatinib is a small-molecule dual inhibitor of the tyrosine kinase activity of epidermal growth factor receptor (EGFR) and HER2. The inhibition of these two pathways can affect tumor growth by reducing the EGFR-dependent proliferative stimulus, by restoring apoptosis, and possibly by enhancing sensitivity to chemotherapy.9,10 However, clinical data so far support the activity of lapatinib in patients with HER2-positive/amplified tumors only.11 Furthermore, this agent can also act against tumoral cells that express the truncated form of EGFR and HER2, which are not recognized by antibodies directed to the external domain.12 In metastatic disease, the combination of lapatinib and capecitabine significantly improved the progression-free survival compared with capecitabine alone in patients pretreated with trastuzumab.13 Therefore, lapatinib in combination with capecitabine has recently been approved for patients with HER2-positive metastatic breast cancer who have progressed on previous therapy including trastuzumab. The combination trastuzumab/lapatinib is also under development because of the potential additive effect of a combined blockade of the outer and inner part of the HER2 receptor; preliminary safety and activity data seem promising.14

On these premises, the combination of lapatinib with chemotherapy and trastuzumab represents an attractive research tool. Therefore, we have designed a phase II randomized trial to evaluate the activity and safety of chemotherapy plus lapatinib, trastuzumab, or both trastuzumab and lapatinib as preoperative therapy for HER2-positive operable breast cancer.

EGF109085-LAP106988/CHERLOB Trial

This is a phase IIb randomized trial in which patients with HER2-positive primary breast cancer stage II-IIIA (tumor size > 2 cm) are randomized to receive chemotherapy plus trastuzumab (arm A), or chemotherapy plus lapatinib (arm B), or chemotherapy plus trastuzumab/lapatinib (arm C). The primary endpoint of this study is the percentage of pCR, defined as complete disappearance of invasive tumor in breast and axillary lymph nodes. Secondary aims are as follows: the percentage of clinical objective responses in the breast; the
Inclusion and Exclusion Criteria

Patients are eligible for this trial if they met the following criteria: previously untreated, infiltrating primary breast cancer of > 2 cm in largest clinical diameter; HER2 positivity (immunohistochemistry [IHC] 3+ or fluorescence in situ hybridization+); age between 18 and 65 years; Eastern Cooperative Oncology Group performance status of 0/1; availability of tumor tissue suitable for biologic and molecular examination before starting primary treatment; left ventricular ejection fraction (LVEF) within the institutional range of normal; normal organ and marrow function; ability to swallow and retain oral medication; and provision of written informed consent. Key exclusion criteria are as follows: stage IIIB, IIIC, and inflammatory breast cancer; presence of distant metastases; uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements; pregnancy or breastfeeding; women of childbearing potential who refuse to adopt adequate contraceptive measures; patients HIV-positive who are receiving combination antiretroviral therapy; gastrointestinal (GI) tract disease resulting in an inability to take oral medication, malabsorption syndrome, a requirement for intravenous alimentation, previous surgical procedures affecting absorption, uncontrolled inflammatory GI disease; and concomitant requirement for medication classified as CYP3A4 inducers or inhibitors.

Sample Size

The sample size has been estimated by using the 2-stage Simon’s design. We assumed that the expected rate of pCR with chemotherapy will be 20%. We will consider worthwhile the combination of chemotherapy plus trastuzumab (arm A) or plus lapatinib (arm B) if the incidence of pCR will be equal to 40%. Moreover, we will consider worthwhile the combination of chemotherapy plus trastuzumab/lapatinib (arm C) if the rate of pCR will be equal to 60%. With α = 10%, β = 10%, the following sample sizes have been obtained: arm A and arm B: first stage 17 patients; if ≥ 4 pCRs are observed, 20 additional patients per arm will be recruited for a total of 37 patients in each arm; arm C: first stage 18 patients; if ≥ 8 pCRs are observed, 28 additional patients will be recruited for a total of 46 patients. Overall, if the hypothesis is fulfilled, a total of 120 patients will be enrolled in the 3 arms.

Trial Design

Patients randomized to arm A receive chemotherapy with weekly paclitaxel 80 mg/m² for 12 weeks followed by 4 courses of FEC (5-fluorouracil [5-FU] 600 mg/m², epirubicin 75 mg/m², cyclophosphamide 600 mg/m²) administered every 3 weeks; arm B (chemotherapy plus lapatinib): stop lapatinib. Reassess after 1 week. If LVEF is below lower limit of normal, repeat LVEF assessment after additional week. If LVEF is above lower limit of normal, restart at reduced dose (1250 mg). If there is no recovery after 2 weeks of holding lapatinib, discontinue lapatinib. Arm C (chemotherapy plus trastuzumab/lapatinib): stop trastuzumab and lapatinib. Reassess after 1 week. If LVEF is above lower limit of normal, resume lapatinib full dose. If LVEF is below lower limit of normal, repeat LVEF assessment after additional week. If LVEF is above lower limit of normal, restart at reduced dose (750 mg). Reassess LVEF 4 weeks from trastuzumab discontinuation. If LVEF is above lower limit of normal, resume trastuzumab. If there is no recovery after 2 weeks of holding lapatinib and/or trastuzumab. If LVEF is above lower limit of normal, resume trastuzumab. If there is no recovery after 2 weeks of holding trastuzumab and/or lapatinib. Reassess after 1 week. If LVEF is above lower limit of normal, restart at reduced dose (1250 mg). If there is no recovery after 2 weeks of holding lapatinib (lapatinib); stop trastuzumab. Reassess after 1 week. If LVEF is below lower limit of normal, repeat LVEF assessment after additional week. If LVEF is above lower limit of normal, restart at reduced dose (1250 mg). If there is no recovery after 2 weeks of holding lapatinib (lapatinib); stop trastuzumab. Reassess after 1 week. If LVEF is below lower limit of normal, repeat LVEF assessment after additional week. If LVEF is above lower limit of normal, restart at reduced dose (750 mg). Reassess LVEF 4 weeks from trastuzumab discontinuation. If LVEF is above lower limit of normal, resume trastuzumab. If there is no recovery after 2 weeks of holding lapatinib and/or trastuzumab. If LVEF is above lower limit of normal, resume trastuzumab. If LVEF is above lower limit of normal, resume trastuzumab if there is no recovery after 2 weeks of holding lapatinib and/or trastuzumab. If LVEF is above lower limit of normal, resume trastuzumab if there is no recovery after 2 weeks of holding lapatinib and/or trastuzumab. If LVEF is above lower limit of normal, resume trastuzumab if there is no recovery after 2 weeks of holding lapatinib and/or trastuzumab.
3 weeks plus trastuzumab 4 mg/kg loading dose followed by 2 mg/kg weekly for the whole duration of treatment (26 weeks). Patients randomized to arm B receive the same chemotherapy regimen plus lapatinib 1500 mg orally daily for the whole duration of chemotherapy. Patients randomized to arm C receive the same chemotherapy regimen plus trastuzumab 2 mg/kg weekly (first loading dose 4 mg/kg) plus lapatinib 1000 mg orally daily for the whole treatment period (Figure 1). Surgery is planned within 2 weeks since the last trastuzumab/lapatinib dose.

**Monitoring of Cardiac Safety**

Only patients with LVEF within the institutional limits of normal at baseline as measured by either echocardiography or multigated radionuclide angiography scan are eligible for this protocol. Left ventricular ejection fraction evaluation is repeated after 12 weeks (before start of the FEC regimen) and at the completion of treatment. More frequent assessment of LVEF should be repeated in any patients with signs or symptoms suspicious of cardiac failure. The rules for the management of asymptomatic decline in the LVEF are summarized in Table 1. A > 16% absolute decrease from baseline in LVEF (asymptomatic or symptomatic), that is below the institution’s lower limit of normal is considered a serious adverse event.

**Gene Expression Profile and Biomarker Evaluation**

To define the inhibition of the downstream pathways of the EGFR family, the following biomarkers are centrally evaluated: EGFR, HER2; pTEN, pAKT, pMAPK; apoptosis (TUNEL test); and Ki-67. These parameters are evaluated by IHC on paraffin-embedded specimens obtained from diagnostic core biopsy of the primary lesion and from surgical specimens. Moreover, fresh tumor tissue from the diagnostic core-biopsy is collected and snap frozen to perform a microarray analysis of the gene expression profile before treatment and to evaluate its correlation with response.

**Conclusion**

This is the first trial exploring the combination of anthracycline-based chemotherapy plus trastuzumab, lapatinib, or both as primary systemic therapy for patients with HER2-positive operable breast cancer. This trial will hopefully provide very useful information for optimizing the use of anti-HER2 agents in early breast cancer.

**References**


