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Original article

Phase II study of liposome-encapsulated doxorubicin plus cyclophosphamide, followed by sequential trastuzumab plus docetaxel as primary systemic therapy for breast cancer patients with HER2 overexpression or amplification

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ABSTRACT

Purpose of the study: Trastuzumab combined with sequential chemotherapy with taxanes and anthracyclines as primary systemic therapy achieved high rates of pathologic complete response (pCR). Non-pegylated liposome-encapsulated doxorubicin (NPLD) has shown equal efficacy but minor cardiotoxicity compared to doxorubicin. This phase II study aimed to evaluate the activity and safety of trastuzumab with sequential chemotherapy for early or locally advanced HER2 positive BC.

Methods: Preoperative treatment included NPLD (60 mg/mq iv) plus cyclophosphamide (600 mg/mq iv) every 3 weeks for 4 cycles followed by docetaxel (35 mg/mq iv) plus trastuzumab (4 mg/mq loading dose iv, then 2 mg/mq iv) weekly for 16 weeks. Primary endpoint was pCR defined as the absence of residual invasive cancer both in the breast and regional nodes. Clinical staging was exploratory evaluated by CT-PET.

Results: 43 pts were treated from december 2005 to September 2011, 39 of them were evaluable for the purpose of study. Median age was 53 years (range: 31–78), the majority of pts had tumour stage cT2 (63%), tumour grade 3 (86%), clinical nodes involvement N+ (77%), ER positive (56%) and Ki-67 $\geq$20% (77%). pCR was reported in 19 (49%) of 39 pts. There was an association between Ki-67 $\geq$20% at baseline and pCR ($p = 0.018$). No cardiac toxicity or discontinuation of trastuzumab was reported. CT-PET modified the clinical stage for 10 patients showing new loco-regional lymph nodes.

Conclusions: This study confirms that integrating anti-HER2 therapy in primary treatment for HER2 positive breast cancer is active. NPLD is a safe option to minimize cardiotoxicity.

Introduction

Preoperative chemotherapy is the standard treatment for locally advanced and inflammatory breast cancer; it is historically adopted to increase the chance for breast conservative surgery. Moreover, neoadjuvant setting allows evaluation of treatment efficacy and identification of subgroups of patients with different prognosis. In particular, irrespective of tumour biology and disease stage at diagnosis, patients achieving a pathologic complete response (pCR) have a better outcome. pCR is now accepted as a surrogate endpoint of treatment efficacy [1–6].

The availability of the anti-HER2 monoclonal antibody trastuzumab (Herceptin™, Roche S.p.A) has significantly improved prognosis in HER2-positive breast cancer patients both in early and advanced disease stages [7–12]. In preoperative setting the addition of trastuzumab to sequential chemotherapy with taxanes and anthracyclines resulted in impressive rate of pCR [13–16].

Anthracyclines constitute the group of most active cytotoxic agents but their efficacy is limited by their cardiotoxicity [17].

More recently, liposomal doxorubicin formulations have shown antitumour efficacy similar to that observed with nonliposomal formulations in first-line treatment of metastatic breast cancer

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(MBC), but with a low cardiac toxicity profile. NPLD (Myocet™, Teva Italia S.r.L.) is a non-pegylated liposome-encapsulated doxorubicin formulation that was designed to improve the therapeutic index of doxorubicin [18].

Using a liposomal delivery system improves the therapeutic ratio of a drug like doxorubicin because the drug can be differentially targeted away from tissues that are susceptible to damage. NPLD is able to directly target tumour sites while sparing healthy tissues [19].

Studies concerning the use of NPLD in first line MBC showed similar activity and efficacy than classic doxorubicin but significant less cardiac and gastrointestinal toxicities, without additional toxicity [18–20]. NPLD is indicated for the first line treatment of metastatic breast cancer in combination with cyclophosphamide. We aimed to investigate the activity and safety of NPLD also in early breast cancer.

Docetaxel (Taxotere™, Sanofi S.p.A.) is one of the most active single-agent drug even if grade 3 or 4 leukopenia occurs in the majority of treated patients. At the time this study started, weekly administration of docetaxel demonstrated comparable efficacy to 3-weekly docetaxel and appeared to have a more favourable toxicity profile [21].

On these premises, we designed a phase II study to evaluate the activity and safety of trastuzumab added to sequential chemotherapy with anthracyclines and taxanes for operable or locally advanced HER2 positive breast cancer patients.

This study also aimed to explore the role of positron emission tomography-computed tomography (TC-PET) in breast cancer staging, prior and after neoadjuvant chemotherapy. Positron emission tomography (PET) using [18F] fluorodeoxyglucose (FDG) has not a well established role for early breast cancer. However, FDG-PET is superior compared to CT scan in detection of internal mammary and mediastinal lymph nodes [22]. Sensitivity, specificity and accuracy for internal mammary and mediastinal lymph nodes were 85%, 90% and 88% respectively for FDG-PET, compared to 54%, 85% and 73% respectively for CT scan [23]. FDG-PET may provide additional information in early stages of breast cancer. Proper staging could modify the prognosis and thus the therapeutic approach.

In addition, we evaluated circulating serum HER-2/neu levels. Since HER-2/neu bearing epithelial cells shed the extracellular domain (ECD) into the serum, serum HER-2/neu levels can be detected by enzyme-linked immunoabsorbent assays (ELISA). Bayer Diagnostics created a HER-2/neu assay that utilizes a monoclonal antibody directed against different epitopes of the HER-2/neu ECD, thereby capturing the protein. The Her-2/neu ECD is proteolytically cleaved from the cellular surface of Her 2/neuoverexpressing tumours and can be detected at increased levels in the sera of patients with Her-2/neu-overexpressing breast cancer [24]. Krainer et al. [25] evaluated 42 primary breast cancer patients prior to any therapy. They observed elevated serum HER-2/neu levels in 14.2% of preoperative patients. In 42.8% of the patients with HER-2/neu tumour expression or amplification serum levels were increased. We therefore used this test to confirm these findings.

Patients and methods

Objectives

Primary objective of our study was to assess pathological complete response (pCR) in breast cancer patients treated with neoadjuvant sequential chemotherapy containing liposome-encapsulated doxorubicin plus cyclophosphamide (MC) every 3 weeks for 4 cycles followed by weekly administration of trastuzumab plus docetaxel (TD) for 16 weeks.

Secondary objectives were clinical response rate (RR), feasibility and tolerability, rate of successful breast-conservation surgery.

The role of 18-Fluorodeoxyglucose (18F-FDG)-PET-CT was studied in the staging of early invasive primary breast cancer before and at the end of treatment. A correlation of response with HER2 serum levels was also investigated.

Selection of patients

Patients with age $\geq$ 18, histologically confirmed HER2-positive (immunohistochemistry IHC 3+ or fluorescence in situ hybridization FISH+) breast cancer, ECOG performance status 0 or 1 and life expectancy >3 months were candidate for participation after signing informed consent.

Neutrophils and platelets had to be $\geq 2 \times 10^9$/L and $\geq 100 \times 10^9$/L respectively. Total bilirubin had to be $\leq$1 time the upper-normal limits (UNL) of the Institutional normal values, ASAT (GOT) and/or ALAT (GPT) had to be $\leq$2.5 UNL). Patients with concurrent ASAT and/or ALAT >1.5× UNL associated with alkaline phosphatase >2.5× UNL were not eligible for the study. Creatinine $\leq$140 mmol/L (1.6 mg/dL).

Normal Left Ventricular Ejection Fraction (LVEF) had to be >50% (evaluated by ultrasonography).

14 ml of blood for determination of HER2 serum levels was collected immediately prior to preoperative treatment and 1–10 days prior to surgery.

Treatment

All patients were scheduled to receive four cycles of Doxorubicin 60 mg/m^2 IV 1-h infusion every 3 weeks plus Cyclophosphamide 600 mg/m^2 IV infusion every 3 weeks followed by 12 cycles of Docetaxel 35 mg/m^2 IV 1-h infusion weekly, with a wash-out period of 7 days every 3 courses (16 weeks of treatment), and Trastuzumab 4 mg/kg IV 90-min infusion loading dose, then 2 mg/kg IV 30- min infusion weekly, for 16 weeks.

All patients received granulocyte colony-stimulating factor as prophylaxis of febrile neutropenia during the MC treatment and in case of neutropenia G2 during TD.

Patients were scheduled to receive adjuvant Trastuzumab 8 mg/kg IV 90-min infusion loading dose, then 6 mg/kg IV 90-min infusion every 3 weeks, for 12 cycles, starting between 4 and 5 weeks after surgery. Patients received radiation therapy and hormonal therapy according to standard practice guidelines. Patients with evidence of progression were treated at Investigator discretion.

All patients received the planned treatment as shown in Fig. 1.

Assessment of endpoints

Pathological and clinical response rate were assessed by Investigator based on the RECIST criteria [26].

Pathological complete response was defined as the absence of residual invasive cancer in the breast and regional lymph nodes determined with standard histologic procedure, also in presence of residual in situ carcinoma.

Clinical tumour and lymph node status were assessed with clinical breast examination, mammography and/or ultrasound. Response to treatment was assessed within 1–2 weeks from the end of treatment by using the same techniques performed at baseline.

The best overall response achieved within the time from drug administration to progressive disease or end of study will be reported.

Histologic breast regression score (RS) were assessed by Investigators according to the German Breast Group and