Integrating bevacizumab, everolimus, and lapatinib into current neoadjuvant chemotherapy regimen for primary breast cancer. Safety results of the GeparQuinto trial


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Background: Safety data for combining bevacizumab, everolimus, or lapatinib with anthracycline- and taxane-based neoadjuvant chemotherapy for breast cancer are limited.

Patients and methods: The neoadjuvant GeparQuinto trial investigates the addition of (i) bevacizumab to four cycles epirubicin/cyclophosphamide (EC) followed by four cycles docetaxel (Taxotere) in patients with human epithelial growth factor receptor (HER2-negative) tumors, (ii) everolimus to weekly paclitaxel in patients with HER2-negative tumors not responding to EC, and (iii) lapatinib instead of trastuzumab to EC–docetaxel in patients with HER2-positive tumors to improve the rate of pathological complete response. Tolerable dose, need for supportive treatments, and early signals for toxic effect were evaluated in a planned safety analysis of 270 patients.

Results: Treatment with chemotherapy plus bevacizumab, everolimus, or lapatinib was discontinued in 23.0%, 25.8%, and 34.5% compared with chemotherapy alone or plus trastuzumab in 19.4%, 24.1%, 3.2%, respectively. More leukopenia, infections, mucositis, and hypertension but less edema was observed by adding bevacizumab; a trend toward more thrombocytopenia, leukopenia, skin changes, and hyperlipidemia by adding everolimus; and more diarrhea, skin changes, and hot flushes but no cardiac events by substituting trastuzumab by lapatinib.

Conclusions: Adding bevacizumab and everolimus to chemotherapy appeared feasible. Lapatinib at 1250 mg resulted in an increased rate of treatment discontinuations and was subsequently dose reduced to 1000 mg.

Key words: bevacizumab, breast cancer, everolimus, lapatinib, neoadjuvant, trastuzumab

Introduction

Anthracycline- and taxane-based chemotherapy is recommended for neoadjuvant systemic treatment (www.ago-online.de). The addition of trastuzumab has almost doubled the pathologic complete response rates in patients with human epithelial growth factor receptor (HER2)-positive breast cancer [1–3].

Within the neoadjuvant GeparQuinto trial, we investigate three distinct treatment approaches for patients with HER2-negative and HER2-positive tumors and for patients with no response to the first chemotherapy cycles [4, 5] by three randomized parallel group comparisons:

- Bevacizumab, an inhibitor of vascular endothelial growth factor pathway targeting tumor neoangiogenesis [6].
- Everolimus (RAD001), an inhibitor of mammalian target of rapamycin, a central protein controlling tumor cell growth and angiogenesis [7].
- Lapatinib, an inhibitor of the HER1 and HER2 receptor tyrosine kinase [8, 9].

As safety data for the combination of these three agents with anthracyclines and taxanes are limited, a run-in safety phase was build into the trial protocol to investigate tolerable dose, need for supportive treatments, and early signals for toxic
effect. We here report the safety results on the first 270 participants included in the run-in phase.

**patients and methods**

**objective**

The aim of the run-in phase of the GeparQuinto trial was to assess the toxic effect and compliance of the combination of bevacizumab with epirubicin/cyclophosphamide followed by docetaxel (EC-D) (Taxotere, Sanofi-Aventis, Berlin, Germany), the combination of everolimus with paclitaxel (P), and the combination of lapatinib with EC-D. For the last combination, the tolerable dose of lapatinib as well as the need of supportive treatment with loperamide and granulocyte-colony stimulating factor (G-CSF) was investigated.

**selection of patients**

We included otherwise healthy female patients with unilateral or bilateral untreated breast cancer histologically confirmed by core biopsy. Only cT4 or cT3 cN+ disease was eligible for the first 60 patients with HER2-negative disease and 60 patients with HER2-positive disease for safety reasons. Thereafter, eligibility was given for all tumor stages if the tumor was estrogen receptor (ER) and progesterone receptor (PgR) negative or restricted to cT2 tumors with clinically positive lymph nodes or cT1 tumors with positive sentinel node biopsy if the tumor was ER or PgR positive. HER2 status had to be available from core biopsy tissue.

**treatment**

An overview of the trial design is given in Figure 1. All patients were scheduled initially to receive EC-D (four 3-week cycles epirubicin 90 mg/m², cyclophosphamide 600 mg/m² and four 3-week cycles docetaxel 100 mg/m²).

Patients with HER2-positive disease were randomly assigned to receive chemotherapy with either trastuzumab (loading dose 8 mg/kg, maintenance dose 6 mg/kg, day 1 of every chemotherapy cycle) or lapatinib (1250 mg/day continuously for 24 weeks starting on day 1 of the first cycle of EC until day 21 of the fourth cycle of docetaxel). The first 30 patients started at a reduced lapatinib dose of 1000 mg/day during the first EC cycle and the first D cycle. Dose was increased on day 1 of the following cycle to 1250 mg/day in case no grade 3 or 4 toxic effect was observed. The first 15 patients received lapatinib together with prophylactic pegfilgrastim on day 2 and loperamide 2×2 mg daily. Loperamide was planned to be dropped for the following 15 patients if ≤1 patient developed grade 3 diarrhea during cycles 1 and 2 of the first 10 patients. Pegfilgrastim was planned to be dropped for the following 15 patients if ≤3 neutropenias grade 4 and ≤1 febrile neutropenia occurred during cycles 1 and 2 of the first 10 patients. If during cycles 1 and 2 of this second cohort, ≤2 diarrheas grade 4, ≤4 neutropenias grade 4, and ≤2 febrile neutropenias occurred, subsequent patients would receive no supportive therapy neither loperamide nor pegfilgrastim and a lapatinib dose of 1250 mg/day would also be given during the first cycle of EC and D.

Patients with HER2-negative tumors were randomly assigned to receive EC-D alone or in combination with bevacizumab 15 mg/kg, day 1 of every chemotherapy cycle. Breast surgery had to be carried out at least 28 days after the last dose of bevacizumab.

In patients without a sonographical response after four cycles EC, bevacizumab treatment was stopped and patients were randomly assigned to instead to P (80 mg/m², once weekly for 12 weeks) with or without everolimus (5 mg orally daily). Treatment with everolimus had to start 21–35 days after the last application of EC with the following dose escalation: day 1, 2.5 mg; day 2, skipped; day 3, 2.5 mg; day 4, skipped; day 5, 2.5 mg; day 6, 2.5 mg; day 7, 2.5 mg; day 8, 2.5 mg; day 9, 5 mg; day 10, 2.5 mg; day 11, 5 mg; day 12, 2.5 mg, and day 13 and thereafter every day 5 mg. Treatment with P started within 7–14 days after the start of everolimus.

**Figure 1.** Trial design and flow of patients through the trial. CR/PR, complete/partial remission; D, docetaxel; EC, epirubicin/cyclophosphamide; HER, human epithelial growth factor receptor; NC, no change; P, paclitaxel.
received the full planned dose. The analysis is mainly descriptive.

assessments
Toxic effect was assessed using National Cancer Institute—Common Terminology Criteria for Adverse Events version 3.0 and reported by the maximum grade per patient.

Tumor response was determined during the third week of the fourth cycle. If a patient showed progressive disease or intolerable toxic effect during EC, patients could skip the remaining EC cycles and continue either with D (+ trastuzumab or + lapatinib) in the case of HER2-positive disease or with P with or without everolimus in the case of HER2-negative disease. Patients underwent surgery within 14 days after completion (i.e. day 21) of the last chemotherapy cycle. Patients with HER2-positive tumor received postoperatively trastuzumab for a total preoperative and postoperative duration of 1 year.

statistical evaluation
It was planned to include all trial participants in this analysis until at least 60 patients were randomly assigned for each comparison. A protocol amendment was foreseen if <75% of patients of any treatment group received the full planned dose. The analysis is mainly descriptive.

results
A total of 270 patients were randomly assigned during the run-in phase, 210 patients with HER2-negative tumor and 60 patients with HER2-positive tumor (Figure 1). Four patients in the HER2-negative group did not start treatment (two due to investigators decision and two due to patient’s request). Of those patients randomly assigned to chemotherapy without bevacizumab, 6 patients discontinued EC, 34 showed no response, and 66 continued with D. Of those allocated to bevacizumab, 2 patients discontinued treatment, 26 showed no response, and 72 continued with D. Without or with bevacizumab was completed in 58 (87.9% of responding patients) and 57 (79.2%) patients, respectively. P was completed in 22 patients (75.9%) without and 23 patients (74.2%) with everolimus. Patients with HER2-positive tumors completed treatment in 96.8% in the trastuzumab group and 65.5% in the lapatinib group (seven discontinued EC-D and lapatinib and additional three completed EC-D but discontinued lapatinib).

Baseline characteristics of patients randomly assigned to the different treatment arms were comparable. One-quarter of patients with HER2-negative disease showed tumors of <5 cm, which were recruited after the initial 60 patients to this setting. HER2-positive tumors were more frequently ductal invasive, high grade, and hormone receptor negative when compared with HER2-negative tumors. Tumors not responding to EC showed similar characteristics except less undifferentiated histology (supplemental Table S1, available at Annals of Oncology online)

Toxic effect combined with a patient’s request to stop treatment was the most frequent cause for treatment discontinuation. Predominantly taxane therapy in combination with the targeted agent was discontinued (15.3% with versus 6.1% without bevacizumab; 16.2% with versus 10.3 without everolimus; and 7.6% with lapatinib versus 0% with trastuzumab). Dose reductions were rarely necessary for EC (≤4%) and P (≤4%), but more frequent during D (<5%). Everolimus was dose reduced in 9.7% and lapatinib in 39.3%, mainly for nonhematological reasons. The percentage of patients receiving >90% of the planned taxane dose was less in all combinations arms compared with the chemotherapy alone arms. At least 90% of the planned dose of bevacizumab, everolimus, and lapatinib was given to 77.0%, 67.7%, and 41.4% of patients, respectively.

Overall, nonhematological grades 3–4 toxic effects were more common during EC or D in combination with bevacizumab compared with EC or D alone (Table 1). Major differences were grades 3–4 leukopenia and infections without neutropenia during EC and mucositis both grades 1–4 and grades 3–4 and hypertension grades 1–4 during D. However, the rate of edema during D was less with bevacizumab compared with without bevacizumab. We observed thrombocytopenia grades 1–2 in 29.2%; however, bleeding was not statistically different with and without bevacizumab. Serious surgical complications have not been documented.

The addition of everolimus to P led only to increases of grades 1–4 leukopenia, grades 1–2 thrombocytopenia, leukopenia, skin changes, and hyperlipidemia (Table 1). Grades 3–4 hematological (18.5% for neutropenia) and nonhematological (10% for mucositis) toxic effects were infrequent with no differences between treatment arms. One patient with preexisting hypertension, diabetes mellitus, left ventricular hypertrophy, and body mass index of 40.7 died after 4 weeks of P and everolimus due to cardiopulmonary failure.

Substituting trastuzumab by lapatinib did not increase hematological toxic effect (Table 1). However, diarrhea, skin changes, and hot flushes were observed more frequently with lapatinib in combination with EC compared with trastuzumab plus EC. No differences for the two anti-HER2 agents were found when given in combination with D. Most frequent grades 3–4 toxic effects with lapatinib were diarrhea during EC and hand–foot syndrome and skin changes during D. Cardiac toxic effect was rare and of low grade in both arms, and no decrease of left ventricular ejection fraction (LVEF) to lower than normal levels was reported.

During the first and second cycle of EC and lapatinib with loperamide and pegfilgrastim prophylaxis, 2 of 10 patients developed neutropenia grade 4, but no febrile neutropenia or diarrhea grades 3–4. In the second cohort without loperamide and pegfilgrastim prophylaxis, four patients developed neutropenia grade 4, one patient febrile neutropenia, and none grades 3–4 diarrhea.

discussion
We here report comparative data on compliance and tolerability of standard anthracycline- and taxane-based neoadjuvant chemotherapy randomly allocated to receive chemotherapy alone or in combination with three different targeted agents. Bevacizumab in combination with EC-D was well tolerated and did not lead to an access of treatment discontinuations compared with chemotherapy alone (26% versus 21.5%). Everolimus plus P after EC pretreatment did not
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*Classified by definition of New York Heart Association.

Bev, bevacizumab; EC, epirubicin/cyclophosphamide; D, docetaxel; Ev, everolimus; H, trastuzumab; L, lapatinib; P, paclitaxel weekly.
show any statistically significant differences in toxic effects compared with P alone. Lapatinib in combination with EC-D did not meet predefined toxic effect criteria for the need of primary prophylaxis with G-CSF but not with loperamide, so that subsequent patients received pegfilgrastim on day 2 and dose of lapatinib was set to 1250 mg for all chemotherapy cycles. However, the high rate of treatment discontinuations with lapatinib (34.5%) compared with the trastuzumab combination (3.2%) was alarming. We reanalyzed data when 77 participants of the GeparQuinto trial had completed lapatinib treatment. Concordantly to the previous analysis, 24 (31.2%) had discontinued neoadjuvant treatment and 19 (24.7%) due to adverse events. Discontinuations became necessary in 9 patients during EC and 15 patients during D. Reasons for discontinuations were nausea/vomiting (n = 7), hand-foot syndrome (n = 6), diarrhea (n = 5), fatigue (n = 4), mucositis (n = 3), other (n = 5) (multiple reasons possible). Subsequently, the protocol was amended introducing a reduction of the lapatinib dose to 1000 mg/day for all cycles, advice a temporary stop and immediate use of loperamide in case of diarrhea grade ≥1, and recommend an early reduction of lapatinib dose in case of intolerability.

Recent reports on lapatinib plus EC or D showed dose-limiting toxic effects leading to dose reductions of the single agents. In a phase I pharmacokinetic study, in 52 patients, the optimally tolerated dose was lapatinib 1250 mg/day and D 75 mg/m² with prophylactic use of pegfilgrastim. However, 75% of patients experienced diarrhea, 50% skin toxic effects, and 32% mucositis at this dose. No pharmacokinetic interaction between the two drugs was detected [11]. Phase I data from the neoadjuvant Lapatax study described dose-limiting toxic effects (neutropenia grade 4 ≥7 days, febrile neutropenia) with lapatinib 1000 mg/day and D 100 mg/m² without growth factor support and with lapatinib 1250 mg/day and D 100 mg/m² applying prophylactic G-CSF [12]. The ChERLOB study investigated a sequence of weekly P followed by four cycles 5-fluorouracil–EC in combination with lapatinib without G-CSF. At the initial dose of 1500 mg/day, grade 3 diarrhea was observed in 20% and with a reduced dose of 1250 mg/day in 15.4% of the patients. Frequent treatment interruptions were still observed due to grade ≥1 toxic effects even at the lower dose, which is comparable with our data [13].

The combination of bevacizumab with adjuvant/neoadjuvant chemotherapy was mainly investigated using adjuvant dose-dense doxorubicin/cyclophosphamide (ddAC)-based regimen and G-CSF support. In the non-randomized Eastern Cooperative Oncology Group, 2104 study patients were sequentially assigned to ddAC followed by P first with and subsequently without bevacizumab. Most common toxic effects were grade 3/4 neutropenia (26%) and grade 3 hypertension (11%). Diastolic dysfunction associated with a decline in LVEF to 40%–50% was observed in two patients receiving bevacizumab and 14% had asymptomatic LVEF declines >10% [14]. In a phase II study including 80 patients receiving bevacizumab in combination with ddAC followed by nab-paclitaxed grades 3–4, toxic effects were fatigue (9.9%), sensory neuropathy (13.6%), mucositis (2.5%), headache (7.4%), and hypertension (13.6%) [15]. Asymptomatic and temporary LVEF decline >15% or >10% was observed in 1.2% and 5%, respectively [16]. Data on the adjuvant use of bevacizumab (15 mg/3 weeks) in combination with AC-D were reported so far in only one preliminary noncomparative study [17], with similar leading toxic effects. The lower rate of edema in the bevacizumab arm corresponds to anecdotal observation on bevacizumab monotherapy to improve long-standing lymphedema. A pilot study demonstrated that bevacizumab acutely decreases interstitial fluid pressure, leading to a decrease in extracellular fluid volume and modest improvement in arm volume [18]. So far, we cannot confirm reports on an increased incidence of surgical complications; however, we intend to collect more detailed information on this subject [19].

Data on combining everolimus with chemotherapy are limited. Daily and weekly doses of everolimus were combined with weekly P in 16 patients with advanced malignancies. Grade 3 neutropenia in two patients met the criteria for dose-limiting toxic effects receiving everolimus 30 mg weekly. Other drug-related grade 3 toxic effects were leucopenia, anemia, thrombocytopenia, stomatitis, asthenia, and increased liver enzymes [20]. Two other phase 1 studies combined everolimus with weekly cisplatin and P in patients with HER2-negative tumors [21] or P and trastuzumab in patients with HER2-positive tumor [22]. Recommended doses were either 5 and 10 mg daily or 30 mg weekly. In subsequent trials, a daily dose of 5 mg everolimus was implemented.

This analysis can only provide a rough estimate on the toxic effect profile due to the small sample size especially regarding the everolimus combination. Exploring neoadjuvant treatments, it cannot provide data on longer treatment durations and chronic toxic effects. The strength of this safety analysis, however, is that it provides comparative data of chemotherapy alone and the same chemotherapy with the targeted agent.

Overall, we concluded from this safety analysis that bevacizumab 15 mg every 3 weeks and everolimus 5 mg/day added to neoadjuvant EC-D or P appeared feasible. The dose of 1250 mg/day of lapatinib in combination with anthracycline- and taxane-based chemotherapy led to an excess of frequent treatment discontinuations and therefore was reduced to 1000 mg/day.

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references


appendix: Investigators of the German Breast Group and Arbeitsgemeinschaft Gynäkologische Onkologie–Brust study group

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