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Combination of bevacizumab and 2-weekly pegylated liposomal doxorubicin as first-line therapy for locally recurrent or metastatic breast cancer. A multicenter, single-arm phase II trial (SAKK 24/06)

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Background: Pegylated liposomal doxorubicin (PLD) and bevacizumab are active agents in the treatment of metastatic breast cancer (MBC). We carried out a multicenter, single-arm phase II trial to evaluate the toxicity and efficacy of PLD and bevacizumab as first-line treatment in MBC patients.

Methods: Bevacizumab (10 mg/kg) and PLD (20 mg/m^2) were infused on days 1 and 15 of a 4-week cycle for a maximum of six cycles. Thereafter, bevacizumab monotherapy was continued at the same dose until progression or toxicity. The primary objective was safety and tolerability, and the secondary objective was to evaluate efficacy of the combination.

Results: Thirty-nine of 43 patients were assessable for the primary end point. Eighteen of 39 patients (46%, 95% confidence interval 30% to 63%) had a grade 3 toxicity. Sixteen (41%) had grade 3 palmar-plantar erythrodysesthesia, one had grade 3 mucositis, and one severe cardiotoxicity. Secondary end point of overall response rate among 43 assessable patients was 21%.

Conclusions: In this nonrandomized single-arm trial, the combination of bimonthly PLD and bevacizumab in locally recurrent and MBC patients demonstrated higher than anticipated toxicity while exhibiting only modest activity. Based on these results, we would not consider this combination for further investigation in this setting.

Key words: bevacizumab, breast cancer, liposomal doxorubicine, phase II, toxicity

introduction

Breast cancer is the most common cancer in women worldwide, with the highest rate of occurrence in Western Europe and North America. It has been estimated that in 2006, there were 429 900 new breast cancer cases in Europe (28.9% of all new cancers) and 131 900 breast cancer deaths (7.8% of all cancer-related deaths) [1]. Five-year survival rates for women with any stage of breast cancer are estimated at ∼80% [2]. Once metastatic disease is detected, median survival ranges between 24 and 30 months [3]. Many improvements have been made in the treatment of metastatic breast cancer (MBC) over the past 5 years, including integration of targeted and biologic agents, new cytotoxic agents, and novel combinations and sequential drug administration. Few regimens have translated into an incremental gain in overall survival (OS) for these patients.

Despite new discoveries, anthracyclines continue to be a mainstay for the treatment of MBC. Pegylated liposomal doxorubicin (PLD; Caelyx, Schering-Plough/Merck) is a novel formulation of doxorubicin. PLD's unique formulation of doxorubicin, encapsulated within liposomes coated with polyethylene glycol, results in prolonged circulation time and decreased cardiotoxicity, alopecia, and myelosuppression, providing an enhanced therapeutic index [4–6]. The side-effect profile of PLD includes mucositis, hand–foot syndrome, and

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mild myelosuppression [5, 6]. A phase III trial of PLD versus doxorubicin as first-line therapy for MBC showed comparable efficacy between the two agents, with reduced cardiotoxicity in the PLD-treated arm [6].

Bevacizumab (Avastin®; F. Hoffmann–la Roche Ltd, Basel, Switzerland) is a recombinant humanized monoclonal antibody to the human vascular endothelial growth factor (VEGF)-A that blocks the binding of human VEGF-A to its receptors. Clinical activity of bevacizumab–chemotherapy combinations has been demonstrated in randomized controlled trials in non-small-cell carcinoma of the lung, colorectal, and renal cell carcinoma [7–9]. In a randomized phase III trial in first-line MBC, bevacizumab in combination with paclitaxel significantly improved response rate (RR) and progression-free survival (PFS) but not OS [10]. The addition of bevacizumab was relatively well tolerated and added only few grade 3 and grade 4 treatment-associated toxic effects. Two as yet unpublished large randomized studies of chemotherapy versus chemotherapy plus bevacizumab in MBC, AVADO, and RIBBON-1 also demonstrate substantially increased RRs and improved PFS when bevacizumab was added to a taxane, anthracycline, or capecitabine [11, 12].

When the trial was initiated, limited data on the combination of bevacizumab and anthracyclines suggested potential for additive toxicity, including cardiac dysfunction [13–15]. In a phase II trial, evaluating the combination of doxorubicin and bevacizumab in patients with metastatic soft tissue sarcoma, conventional doxorubicin was shown to be associated with unacceptable cardioxicity [13]. Subsequently, PLD was substituted for conventional doxorubicin and evaluated in combination with bevacizumab in sarcoma patients [14]. Mucositis and skin toxic effects were dose limiting with the combination using a PLD dose of 45–50 mg/m^2 every 4 weeks. Therefore, a PLD dose reduction to 22.5 mg/m^2 every 2 weeks was implemented and recommended for future trial of the combination [14]. We initiated a multicenter, single-arm phase II trial to evaluate the toxicity and efficacy of PLD and bevacizumab as first-line treatment for patients with MBC.

methods

patients

Eligible patients had cytologically or histologically proven metastatic or locally recurrent inoperable erbB2-negative breast cancer. Other inclusion criteria included tumor not amenable to radiotherapeutic treatment, measurable disease according to RECIST criteria [16], left ventricular ejection fraction (LVEF) ≥55%, World Health Organization performance status zero or one, no previous chemotherapy for metastatic or inoperable locally recurrent breast cancer, and low-risk factors for bleeding (e.g. normal coagulation parameters, no concomitant treatment with anticoagulants, sufficient interval from surgical procedures). Exclusion criteria included previous adjuvant or neoadjuvant chemotherapy within 12 months before registration; previous therapy with bevacizumab or other anti-VEGF drug; cumulative doxorubicin dose of >360 mg/m^2 or epirubicin >720 mg/m^2; epirubicin as neoadjuvant or adjuvant treatment; known central nervous system (CNS) metastases; severe cardiovascular disease; tumor amenable to radiotherapy; or history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess.

trial design

SAKK (Schweizerische Arbeitsgemeinschaft Klinische Krebsforschung) sponsored this prospective, single-arm, multicenter phase II trial of bevacizumab in combination with PLD in patients with inoperable locally recurrent or MBC. Patients were treated with PLD 20 mg/m^2 i.v. on days 1 and 15 of each 4-week cycle for a maximum of six cycles or until an event qualifying for discontinuation occurred. Patients received bevacizumab 10 mg/kg i.v. on days 1 and 15 of each 4-week cycle for six cycles in combination with PLD and as monotherapy thereafter. PLD and/or bevacizumab were to be discontinued for progressive disease (PD), unacceptable adverse reaction, patient refusal, or physician withdrawal.

The primary end points were severe cardiac toxicity or grade 4/5 and selected grade 3 nonhematological toxicity of the treatment combination. Severe cardiac toxicity was defined as symptomatic deterioration to New York Heart Association (NYHA) III or IV; concomitant with an LVEF drop by >10% points from baseline to <50% LVEF; or cardiac death due to heart failure, myocardial infarction or arrhythmia, and probable cardiac death defined as sudden, unexpected death within 24 h of a definite or probable cardiac event. Grade 4/5 and selected grade 3 nonhematological toxic effects were defined as any nonhematological adverse drug reaction of grade 4/5 according to NCI CTCAE v3.0 or any of the following grade 3 adverse drug reactions: palmar-plantar erythrodysesthesia (PPE), cognitive disturbance, CNS hemorrhage, and mucositis/stomatitis. These toxic effects were selected because of their assumed relatively high likelihood of occurrence with this drug combination and their severe impact on the quality of life of affected patients.

Secondary end points included mild to moderate cardiac toxicity, time to cardiac toxicity, time to grade 4/5 and selected grade 3 nonhematological toxicity, overall response [complete response (CR) plus partial response (PR) as determined by RECIST criteria] [16], time to treatment failure, duration of response (DR), PFS, OS, and adverse events. Mild to moderate cardiac toxicity was defined as an LVEF drop by >10% points from baseline to <50% LVEF, with asymptomatic or only mildly symptomatic deterioration of cardiac disease (NYHA I–II), confirmed by a second LVEF assessment after 4 weeks. Time to cardiac toxicity and time to grade 4/5 and selected grade 3 non-hematological toxicity were calculated from registration to first documented occurrence.

Before treatment, at the end of cycles 2, 4, and 6, and every 3 cycles thereafter until disease progression, tumor assessment for objective response was carried out using computed tomography, magnetic resonance imaging, or conventional X-ray/ultrasound techniques. Lesions were assessed using the same method on each occasion. Wherever possible, lesions were measured or evaluated by the same clinician/radiologist at each assessment visit. Any objective response (CR or PR) had to be confirmed after a minimum of 4 weeks.

statistical methods

The statistical design was based on assumptions on the primary end point of severe cardiac toxicity, and selected grade 3 and grade 4/5 non-hematological toxicity manifested during the first six treatment cycles (or until 6 months after enrollment if the treatment had to be stopped before reaching six cycles). Using Simon's two-stage optimal design to compute stage I and stage II sample sizes, a proportion of selected toxic events of ≥33% was considered unacceptable, while ≤15% was considered acceptable, in which case, the trial treatment would be proposed for further investigation. For 5% significance level and 80% power, 14 patients were needed in the first stage and additional 29 patients for the second stage. Hence, a maximum of 43 assessable patients were needed.

To allow continuation of patient accrual while waiting for the results of the stage I analysis, the design was modified by Herndon's [17] approach. At final analysis, the treatment would not be considered interesting for

further investigation, if 9 or more among the 43 patients experienced the selected toxic events; otherwise the treatment would be considered as promising for further investigation.

The results were summarized by toxicity rate and 95% Pearson–Clopper confidence interval (CI).

Patients who discontinued treatment before completing the first two treatment cycles and who did not experience any of the defined toxic effects were not considered assessable for the primary end point. For all other end points, all treated patients (i.e. who received at least one dose of study medication) were considered assessable. Safety parameters were analyzed and summarized in tables. Time-to-event end points were assessed at the end of the trial and estimated by the Kaplan–Meier method. Data analysis was carried out using SAS 9.1 (SAS Institute Inc., Cary, NC) and S-Plus 8.0 (Insightful Corp., Seattle, WA).

ethical considerations

The trial was carried out in accordance with the declaration of Helsinki, the Guidelines of the Good Clinical Practice, and the requirements of the local ethical committees. The respective ethics committees of participating centers had given approval to the trial. Written informed consent was obtained from all patients before registration. This study is registered with ClinicalTrials.gov, number NCT00445406.

results

patients

Between 25 January 2007 and 20 March 2008, 43 patients were enrolled. Patients' baseline characteristics are listed in Table 1. Of the 43 patients, 2 had locally recurrent disease only, all others had metastatic disease, and 81% and 53% of patients had received previous hormonal and/or (neo)adjuvant chemotherapy, respectively. The mean treatment duration was 5.2 months (median 4.3 months, range 0.5–19.4 months), 182 cycles of PLD (median per patient 5, range 1–8) and 247 cycles of bevacizumab (median per patient 5, range 1–21 months) were administered. Two patients continued treatment beyond PD for 3 and 6 months, respectively. PLD had to be reduced, delayed, or omitted during 109 cycles, almost exclusively due to toxicity. Bevacizumab had to be delayed or omitted during 61 cycles, mainly due to toxicity (28 cases) or to patients' request (15 cases). Median follow-up was 15.0 months.

safety

According to the predefined rules of the Herndon's approach, the trial had to be stopped prematurely after the enrollment of 43 patients, although 4 patients did not complete two cycles of therapy and therefore were not assessable for the primary end point. Among the 39 fully assessable patients, 16 (41%) had grade 3 PPE, including 2 patients with additional grade 3 mucositis. One patient (2.3%) had grade 3 mucositis and one patient (2.3%) had grade 3 cardiac decompensation. Thus, 18 of 39 [46%, 95% CI 30% to 63%] patients were classified as failures with respect to the primary end point (Table 2).

These toxic events occurred after a median of 2.9 months (range 1–21 months), 13 of the 17 noncardiac events occurred before the end of the fifth month of therapy. The only cardiac toxicity seen in this trial occurred 4.7 months after treatment initiation. No mild cardiac events occurred. The most frequent grade 2 toxic effects were PPE ($n = 15$), mucositis ($n = 14$), fatigue ($n = 5$), hypertension ($n = 4$), and pain ($n = 4$). Twenty-five patients stopped treatment due to PD, nine due to unacceptable toxic effects of the bevacizumab/PLD combination therapy, but no patient died during treatment.

Table 1. Patient characteristics at baseline

	N (%)
Performance status WHO	
0	26 (60)
1	17 (40)
Previous therapies	
Surgery	41 (95)
Radiotherapy	35 (81)
(Neo)adjuvant chemotherapy	23 (53)
Hormonal/endocrine	35 (81)
None	1 (2)
Echocardiogram: abnormal findings	
Missing	1 (2)
No	34 (79)
Yes	8 (19)
Echocardiogram: description of abnormal findings	
Hypertensive cardiac disease	1 (2)
Left ventricular relaxation disturbances but normal LVEF (57%)	1 (2)
Minimal enlarged left atrium. Minimal mitral valve insufficiency	1 (2)
Minor aortic insufficiency	1 (2)
Pericardial effusion, not hemodynamically relevant	1 (2)
Relaxation dysfunction	1 (2)
Bicuspid aortic valve, minimal tricuspid insufficiency	1 (2)
NYHA classification	
0	36 (84)
1	7 (16)
Hormone receptor status	
Negative	9 (21)
Positive	34 (79)
Stage of disease at baseline	
Locally recurrent only	2 (5)
Metastatic	41 (95)
Menopausal status	
Missing	1 (2)
Premenopausal	4 (9)
Postmenopausal	28 (65)
Other, age <50	2 (5)
Other, age ≥50	8 (19)

LVEF, left ventricular ejection fraction; WHO, World Health Organization

Table 2. Toxicity

Toxicity	Patients (total evaluable $N = 39$), *n* (%)
Grade 3 PPE	16 (41.0)
Grade 3 mucositis	1 (2.6)
Severe cardiotoxicity	1 (2.6)
Grade 3/4 events	18 (46.2)

PPE, palmar-plantar erythrodysesthesia.

efficacy

Among the intention-to-treat population of 43 patients, clinical benefit rate (PR and stable disease) was 73% (31 of 43; 95% CI 56% to 85%), but only 21% (9 of 43; 95% CI 10% to 36%) had a PR (Table 3). During follow-up, 32 patients had PD or died and thus were counted as events for PFS. Nine patients started second-line treatment without PD and are censored for this end point, possibly introducing a positive bias. Median PFS was 5.7 months (95% CI 4.6–8.1; Figure 1). Among the nine patients with response, the mean response duration was 4.9 months and median time to response was 3.6 months. Since four of these patients are still without PD, the mean response duration will increase with continuing follow-up. Eighteen patients have died, yielding a median OS of 15.9 months (95% CI 14.0–21.5). The estimated 1-year survival rate is 69% (95% CI 52%–81%).

discussion

There is no generally accepted, optimal first-line chemotherapy regimen for MBC; however, the use of a taxane and an anthracycline, either as monotherapy or in combination, is considered appropriate therapy [18, 19]. Studies comparing single-agent therapy with combination chemotherapy have yielded conflicting results [20, 21]. While most of these studies have shown increases in RR and PFS, and some have even shown a benefit in OS with combination regimens, toxicity was generally more severe in the combination therapy [20, 22].

Novel drug combinations that improve efficacy without additional toxicity are urgently needed. Recently, antiangiogenic treatment with bevacizumab, a monoclonal antibody against VEGF, was shown to improve chemotherapy efficacy in first-line MBC in three large randomized trials [10–12]. Cardiotoxicity of anthracyclines has been shown to be increased by several targeted therapies, such as trastuzumab [24], sunitinib [25], sorafenib [26], and others. When the trial was planned, there was also concern that bevacizumab might increase the cardiotoxicity of anthracyclines [13, 15]. These results prompted our phase II study of bevacizumab with a cardiac-sparing agent, PLD, that is active in the treatment of MBC [6, 23].

Table 3. Best response to bevacizumab/pegylated liposomal doxorubicin

Best response	Patients (total evaluable $N = 43$), n (%)
Partial responses	9 (21.0)
Stable disease	22 (51.2)
Progressive disease	10 (23.3)
Not evaluable	2 (4.6)

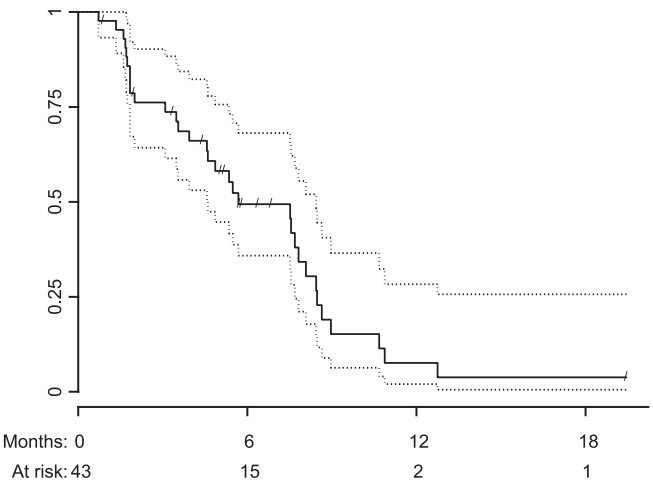

Figure 1. Kaplan–Meier curve (including pointwise 95% confidence interval) showing progression-free survival.

Results of a randomized trial comparing doxorubicin and PLD as first-line treatment of women with MBC showed comparable PFS (7.8 versus 6.9 months) and OS (22 versus 21 months) between treatment arms [6]. The overall RR associated with PLD was 33% in the 209 patients who had measurable disease [6]. The RR in our first-line trial of PLD and bevacizumab in 43 patients with MBC was only 21% and hence not superior to RRs seen in trials of PLD monotherapy in the same setting. Similarly, additional phase II trials evaluating PLD in the second- and third-line MBC setting showed objective RRs between 13% and 31% [27–29]. The RR in our trial is disappointing in light of the fact that in all randomized comparisons of chemotherapy versus chemotherapy plus bevacizumab in first-line MBC, an increase in RRs was observed in the combination arms [10–12]. Although cross-trial differences in patient populations might account for some of the differences in RR seen, and although our trial was too small to draw firm conclusions on efficacy, it clearly does not suggest additive activity of PLD and bevacizumab.

However, the most important finding of our trial was the relatively high rate of grade 3 PPE (41.0%) and mucositis (2.6%). PPE is a dermatologic toxicity that occurs relatively frequently in association with prolonged exposure to cytotoxic drugs, either because of a relatively long half-life of the drug (e. g. PLD) or because of continuous application, either orally (e.g. capecitabine) or by continuous intravenous application (e.g. 5-fluorouracil, doxorubicin). Although the pathophysiology of PPE in PLD-treated patients is not well understood, PLD has been detected in elevated concentrations in eccrine sweat glands in palms and soles, where it accumulates perhaps due to the hydrophilic coating of liposomes [30]. The higher number of eccrine glands in the hands and feet could explain the preferred localizations of the syndrome.

In two registrational trials of PLD [6, 31], where the dose of PLD was 50 mg/m^2 every 4 weeks, the rate of grade 3 PPE was 17%–18%. Although in this trial, a lower dose of PLD (20 mg/m^2) administered every 2 weeks was utilized, the rate of grade 3 PPE was 41%. Indeed, the rate of grade 3–4 PPE observed in our trial was unusually high relative to other MBC observational studies (6%–17%) [32, 33].

Despite the relatively small number of patients treated in our trial and the inherent difficulties of cross-trial comparison, our findings are suggestive of an additive toxic effect of bevacizumab and bimonthly PLD with respect to PPE. This conclusion is also supported by a small trial resulting in dose-limiting mucositis and skin toxicity in 9 of 12 sarcoma patients treated with the same schedule of bevacizumab and PLD used in our trial [14]. Possible mechanisms of action of

a hypothetical synergistic toxicity include (i) a direct pharmacological interaction between PLD and bevacizumab; (ii) a specific effect of bevacizumab on the vasculature of soles, palms, and possibly the oral mucosa, leading to increased accumulation of PLD; and (iii) interference of bevacizumab with wound healing of dermal and mucosal injuries. It is notable that the addition of bevacizumab to capecitabine, a drug with potential antiangiogenic properties that frequently causes PPE, did not seem to substantially increase PPE in the randomized RIBBON-1 trial. This suggests a different interaction of bevacizumab with capecitabine than with PLD or a different mechanism of capecitabine-induced PPE [12].

In two recent phase I dose escalation studies in advanced solid tumors, a doubling of the incidence of PPE was reported after addition of bevacizumab to sorafenib, a raf-kinase inhibitor, which interferes with the VEGF receptors 1 to 3 and other kinases [34, 35]. Sorafenib monotherapy is known to cause PPE in ~20% of treated patients, and PPE in these studies was associated with cumulative sorafenib dose. However, since no difference in sorafenib serum concentration between single-agent and dual-drug therapy was demonstrated, the authors concluded that not a pharmacokinetic interaction but the anti-VEGF properties of the two drugs must have been the reason of the synergistic skin toxicity observed [34].

In conclusion, we studied the combination of PLD and bevacizumab in 43 patients with MBC and observed a high rate of toxicity with modest activity. Based on these results, we would not consider the combination of PLD 20 mg/m^2 and bevacizumab 10 mg/kg on days 1 and 15 every 4 weeks, for further investigation in these patients.

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The companies were involved in trial design, but had no role in data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data and the final responsibility to submit for publication.

contributors: CR wrote the study protocol in collaboration with members of the SAKK Coordinating Center, Bern including RH, SL, BC, and MM. CR, TR, CS, JH, MB, MF, RM, RW, DR, AM, MM-H, RH, and KZ enrolled patients to the study. TS was responsible for the evaluation and interpretation of cardiac toxicity data. BC and SL collected study data. MM did the statistical analyses of the study data. CR wrote the manuscript on behalf of all authors. All authors have approved the manuscript and any revisions.

disclosures

CR has served on advisory boards for Roche. RH has received research grants from Roche. The other authors declared no conflicts of interest.

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