Preoperative chemotherapy for operable breast cancer has been evaluated in a number of series. The recombinant humanized anti-human VEGF monoclonal antibody (rhuMAb, bevacizumab) inhibits several activities of VEGF, including endothelial cell growth, vascular permeability and angiogenesis. Synergy with many cancer chemotherapeutic agents, was observed in preclinical studies and in phase I and phase II trials and confirmed in phase III trials. Bevacizumab has also been tested in breast cancer in the neoadjuvant setting with encouraging results. Based on the synergism of bevacizumab in combination with chemotherapy, we will investigate the efficacy of bevacizumab in modulating the proliferation rate of locally advanced operable breast tumors treated with primary therapy.

**Key words:** primary chemotherapy, breast cancer, rhuMAb, bevacizumab

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women (IMPACT) confirmed the superiority of the aromatase inhibitor, although this was limited to the rate of breast conserving surgery [10]. These results further strengthen the requirement of designing new trials of primary therapy to address different preoperative strategies according to baseline pathological features of the tumor.

Both capecitabine and vinorelbine have been extensively studied and have been shown to be highly active in the treatment of advanced breast cancer. The combination of the two drugs has been investigated in phase I and II trials with response rates ranging from 30% to 68%. In a previous study, we found a 75% cCR and a 12% pCR rate, with breast conserving surgery performed in 67%, by using a non-anthracyclin-based regimen, containing vinorelbine in combination with fluorouracile either by bolus (FLN) or as a continuous infusion with cisplatin (ViFuP). Chemotherapy was given for up to six cycles and was associated with endocrine therapy with 3-month triptorelin + letrozole or letrozole alone, according to menopausal status. The combination of vinorelbine combined with capcitabine represents an attractive alternative because the use of capcitabine mimics the infusional administration of fluorouracil, thus increasing the activity of this regimen compared with bolus 5-FU.

According to our previous experience, six courses of the ECF regimen (epirubicin, cisplatin and continuous infusion fluorouracil) yielded a high rate of both clinical and pathological response in endocrine unresponsive breast cancer as previously shown by Smith [11]. A number of trials reporting either final or preliminary results, indicate that the sequential addition of a taxane to an anthracycline-based induction regimen led to an improvement of pCRs and also of overall survival, in one small trial, compared with eight cycles of the same anthracycline-containing regimen [12]. Therefore, we have decide to add a taxane to our standard ECF in order to prolong the duration of treatment and to use a sequence of anthracyclines and taxanes. Patients will thus receive four cycles of ECF followed by 3 months of weekly paclitaxel, which is supposed to be superior to the 3-week schedule as of tolerability and efficacy.

bevacizumab: mechanism of action and clinical activity in breast cancer

Vascular endothelial growth factor (VEGF) is the most potent and specific angiogenic factor and has been identified as a crucial regulator of both normal and pathological angiogenesis. The recombinant humanized anti-human VEGF monoclonal antibody (rhuMAb, bevacizumab) inhibits several activity of VEGF, including endothelial cell growth, vascular permeability and angiogenesis (13–14). In preclinical research, activity was demonstrated in different tumor models, such as glioblastoma, leiomyosarcoma, colon cancer and breast cancer. Moreover, synergy with many cancer chemotherapeutic agents was observed in preclinical studies and in phase I and phase II trials and confirmed in phase III trials. Bevacizumab both alone and in combination with chemotherapy was well tolerated, with hypertension, proteinuria, thrombosis and bleeding being the most commonly reported toxicities [13, 14]. Co-administration of bevacizumab with cytotoxic chemotherapy did not appear to result in a change in the systemic concentrations of the cytotoxic agents.

Two phase I clinical trials of bevacizumab have been reported. In the first trial, bevacizumab was administered to 25 patients with refractory solid tumors at doses ranging from 0.1 to 10 mg/kg [15] over 6 weeks. In the second trial, bevacizumab, at a dose of 3 mg/kg, was administered in combination with chemotherapy to 12 patients with advanced cancer [16]. Those trials showed that bevacizumab can be administered safely, without dose-limiting toxicities, at doses up to 10 mg/kg and that it can be combined with chemotherapy without apparent synergistic toxicity. All patients who completed 6–12 months of therapy in the phase I/II trials of bevacizumab were given the opportunity to participate in an ongoing extension study [17] in solid tumors. Of 52 patients with advanced solid tumors, 28 received bevacizumab for 1 year or more. The dosage of bevacizumab ranged from 5 to 15 mg/kg every 2 or 3 weeks. The majority of patients treated for 1 year had an observation period off therapy for up to 6 months, but were able to restart bevacizumab at progression. Sixteen patients progressed on or before the observation period and restarted bevacizumab. The median duration of treatment was 14 months (range 11–36 months) and, at the time of reporting these results, a median survival time had not been reached (range 17 months to >40 months, with 20 patients alive). Safety results obtained from the extension study indicate that the adverse event profile of bevacizumab when used long-term differs from that seen with cytotoxic chemotherapy. Bevacizumab was generally well tolerated, with no unexpected adverse events observed after 1 year of therapy. The only significant events that occurred during the extension study were thromboembolic episodes (five cases of deep vein thrombosis). Grade 2/3 hypertension developed in three patients and grade 1 proteinuria occurred in one patient. There were also two gastrointestinal bleeds (grades 2 and 4) in patients who had colorectal cancer. Overall, the data obtained from the extension study suggest that some patients who progress after 6–12 months of bevacizumab, with or without chemotherapy, may benefit from retreatment.

The pharmacokinetic profile of bevacizumab indicates that sustained levels can be maintained with administration once every 2–3 weeks. The schedules of administration in the phase II studies in breast cancer and in the phase III studies in colorectal cancer were similar: 10 mg/kg every 2 weeks versus 15 mg/kg every 3 weeks, respectively. For patient’s convenience, it is suggested that the administration of bevacizumab is linked with the infusion of chemotherapeutic drugs.

A phase II, two-center, open-label clinical trial of bevacizumab monotherapy produced encouraging results in patients with breast cancer [18]. Seventy-five patients with metastatic breast cancer were treated with bevacizumab at escalating doses of 3 mg/kg (n = 18), 10 mg/kg (n = 41) and 20 mg/kg (n = 16) administered intravenously every other week. The majority of patients (83%) had infiltrating ductal carcinoma and 96% had received prior anthracyline- or taxane-based therapy for metastatic disease. Twenty-one of the 75 (28%) patients were HER2-positive and 47 (63%) were HER2-negative. Twelve of the 75 patients (16%) completed the 6-month trial and received all 13 scheduled doses of bevacizumab. The median number of doses of bevacizumab
administered was six and the median duration of treatment was 70 days. Objective responses were documented in seven of 75 (9.3%; 6.7% confirmed) patients. The median duration of confirmed response was 5.5 months (range 2.3–13.7 months), with one ongoing partial response at 10 months. At the final tumor assessment on day 154, 12 of 75 (16%) patients had stable disease or an ongoing response. In the 10-mg/kg group, 17% of patients had stable disease or better at day 154 and 7% were stable at 1 year. Thus, the optimal dosage of bevacizumab in that trial was to be 10 mg/kg every other week, and toxicity was deemed to be acceptable as only four patients (5.3%) stopped bevacizumab because of adverse events. Four patients treated at a dose level of 20 mg/kg had headaches with nausea and vomiting that were considered to be dose limiting, but this did not occur at the lower dose levels. Proteinuria was noted in 17 of 72 (24%) evaluated patients, and three patients developed significant proteinuria, including two with nephrotic syndrome. No significant cases of bleeding were reported in that trial or in patients with breast cancer in earlier trials of bevacizumab, although bleeding (typically mild epistaxis) occurred in 25% of patients.

A phase II trial of bevacizumab with vinorelbine is examining patients with metastatic breast cancer. Key eligibility criteria include prior chemotherapy with one or two regimens for metastatic breast cancer (including trastuzumab for HER2-positive disease) and disease progression within 1 year of adjuvant chemotherapy. Patients receive treatment with bevacizumab at a dose of 10 mg/kg every 2 weeks and vinorelbine at a dose of 25 mg/m²/week (adjusted for neutrophil count) until either the disease progresses or they experience undue toxicity. The trial has observed 17 responses (one complete and 16 partial) among 55 patients [31% objective response rate (ORR)]. Overall, bevacizumab with vinorelbine was well tolerated, and toxicity analyses indicate only minor occurrences of hypertension, proteinuria and epistaxis and one instance of pericardial effusion. No major bleeding events or thrombotic events were noted and other side-effects were consistent with the historic experience of the use of vinorelbine [19].

The bevacizumab phase III clinical trial for breast cancer was an open-label, randomized, comparative trial in which previously treated patients with metastatic breast cancer were randomized to treatment with either capecitabine alone or capecitabine plus bevacizumab [20]. From November 2000 to March 2002, 462 patients entered the study. The bevacizumab dosage was 15 mg/kg once every 3 weeks. Capecitabine was given at the US Food and Drug Administration-approved dose of 2 500 mg/m² in two divided doses for 2 out of every 3 weeks, with appropriate dose reductions for toxicity. Eligibility included resistance to both anthracyclines and taxanes and one or two prior chemotherapy regimens for metastatic disease. Patients with evidence of disease progression within 1 year of adjuvant therapy containing both an anthracycline and a taxane were also eligible. This very-poor-prognosis group of patients represented about 20% of the patients in the trial. HER2-positive patients were excluded unless they had received prior trastuzumab therapy. Also excluded were patients with significant proteinuria. Although adding bevacizumab to capecitabine produced a highly statistically significant greater ORR (19.8% versus 9.1%), the primary end point of the study, there was no effect on progression-free survival (PFS).

Responses to bevacizumab tended to be short and, therefore, were not translated into improved PFS times, which were equivalent at 4.9 months in the combination arm and 4.2 months in the capecitabine-alone arm. No increases in capecitabine-related toxicities or serious adverse events were noted in the bevacizumab arm, and the pattern of bevacizumab-related adverse events was similar to that seen in phase II trials.

In a phase III study in 462 patients with refractory and heavily pretreated metastatic breast cancer, bevacizumab, administered at a dose of 15 mg/kg every 3 weeks, doubled the response rate obtained with single-agent capecitabine (19.1% versus 9.1%) but did not affect the survival (4.86 months versus 4.17 months) [11]. Recently, a phase III randomized trial which compared paclitaxel to a combination of bevacizumab plus paclitaxel as first-line treatment of metastatic breast cancer reported an increased objective response rate (28.2% versus 14.2%) and improved PFS with bevacizumab and paclitaxel [21].

**bevacizumab as primary therapy of breast cancer**

Bevacizumab has also been tested in the neoadjuvant setting with encouraging results. In a first trial patients with inoperable locally advanced breast cancer received docetaxel with or without bevacizumab with five clinical CR and 24 PR [22]. Wedam et al. [23] recently reported the results of the combination of bevacizumab with doxorubicin and docetaxel for the treatment of inflammatory breast cancer. After the completion of therapy (one cycle with bevacizumab alone followed by six courses of the combination), eight of 13 patients experienced a confirmed PR, with evidence of a decrease in vascular permeability on dynamic contrast-enhanced MRI.

A set of studies of primary therapy exploring the activity of different regimens according to endocrine responsiveness has been designed at our institute due to the confirmed role of baseline pathological features of the tumor in predicting the responsiveness to primary therapy. The aim of administering systemic therapy prior to surgery is to make a locally advanced tumor operable or to allow conservative surgery in the case of a T2–T3 tumor. Treatment is thus expected to induce a maximum tumor shrinkage within a short period (usually 3–6 months) [24–26]. Moreover, the decay of Ki-67 expression has proved to be significantly associated with response to primary chemotherapy [6, 7]. In our institution we will investigate the efficacy of bevacizumab in modulating the proliferation rate of locally advanced operable breast tumors treated with primary therapy according to endocrine responsiveness. The primary objective of the study is to estimate the effect of bevacizumab compared with no bevacizumab on the change in tumor cell proliferation by assessment of Ki-67, a biomarker of cell proliferation, in breast cancer tissue at baseline (tumor core biopsy) and after 24–28 weeks (surgical resection specimen) of treatment.

Patients with histologically proven primary breast cancer >2.0 cm (T2–T4 a–d, N0–2, M0), ER PgR and c-erbB-2 expression defined according to EIO guidelines and no
treatment with previous chemotherapy/endocrine therapy were enrolled in a phase II randomized study to investigate the effects of bevacizumab on cell proliferation and on pCR in patients with locally advanced operable breast cancer. Patients will be randomized to receive chemotherapy alone (with or without endocrine therapy) or a combination of chemotherapy (with or without endocrine therapy) combined with bevacizumab. Patients with endocrine responsive breast cancer T2–T4a–c or T4d (irrespective of endocrine responsiveness) with a core biopsy (ER and PgR ≥10%) will receive chemotherapy with a low-toxic regimen including capecitabine and i.v. vinorelbine q. 21 days for eight courses combined with endocrine therapy with GnRH analogue and letrozole (at the achievement of serum 17-betaestradiol within range of menopausal) if premenopausal, or letrozole alone if postmenopausal. Patients with endocrine unresponsive breast cancer (T2–T4a–c) or T4d (irrespective of endocrine responsiveness) will receive four courses of ECF regimen followed by weekly paclitaxel for 3 months. Bevacizumab will be administrated at a dose of 15 mg/kg every 21 days for eight courses. Patients with overexpression HER2/neu (3+) or amplification of HER2/neu gene evaluated by FISH, suitable for herceptin-containing regimens as primary therapy, will be excluded. This study will provide further information and knowledge about primary surgery.

**references**


