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Bevacizumab-based Treatment in Breast Cancer (BC) Patients With Cutaneous Metastases − a Subgroup Appropriate for Targeting Angiogenesis?

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Background:The value of targeting angiogenesis in BC has recently been questioned. Therefore, the identification of subgroups that might benefit from targeting angiogenesis is needed. Bevacizumab (BEV), the first inhibitor of angiogenesis, has been shown to improve outcome in metastatic BC. The results from patients with BC and skin dissemination are presented here.
Patients and Treatment: From 105 patients (pt) with advanced BC treated with BEV/paclitaxel (95pt) or BEV/docetaxel (10pt), 30pt (29 Female/ 1 Male, 33−75 years old, with median age 52 years) with cutaneous metastases exclusively [3pt] or in combination with other sites of metastases [27pt], were separately studied. In 9pt had extensive lymphatic dissemination while in 8pt de novo inflammatory BC with skin dissemination was present. Forteen and 16 pts were treated in 1st and 2nd line respectively.
Results: The overall response rate was 55%, 38% in 1st and 2nd line treatment respectively. Although complete clinical remission was not achieved in pt with cutaneous metastases, a major PR in 13/14 pt and 15/16 pt treated with 1st and 2nd line treatment respectively (dissociated response in 19pt) for >12 months in the majority of patients was observed. Yet, rechallenge of BEV in 1pt after a long BEV-free interval resulted in a new remission. All patients with inflammatory breast cancer responded (cPR, no pCR).
Conclusions: Although the small number of patients does not allow for firm conclusions, the almost uniform response observed in our patients with BC and cutaneous metastases (28/30pt, 93.3%) should be mainly attributed to BEV, given that the usual response rate to cytotoxics either in monotherapy or combinations is clearly inferior. Moreover, the dissociated response observed in 63% of patients corroborates this statement. If these findings are confirmed in more patients and by others, a subgroup of patients with advanced BC with antiangiogenic treatment "sensitivity" may emerge.
Also, the identification of predictive markers for targeting angiogenesis may be incited from such observations using prospective studies.

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Lapatinib (L) in Combination With Paclitaxel (P) is an Effective and Tolerable Treatment in HER2-overexpressing Metastatic Breast Cancer (MBC) Patients

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Background: The recently completed phase III randomized, double-blind EGF104535 study compared lapatinib plus paclitaxel (L+P) versus P alone in patients with HER2-positive (MBC). The study was conducted in the Asian-Pacific, Eastern European and South American regions.
Methods: Pts with centrally confirmed HER2-positive (FISH) MBC and measurable disease were randomized to L 1500 mg daily + P 80 mg/m^2/wk 3 out of 4 wk or to P 80 mg/m^2/wk 3 out of 4 wk alone. Pts were administered P for 6 cycles with additional cycles at investigator discretion, and continued on blinded randomized therapy until disease progression (PD). At time of PD, there was an optional monotherapy extension to allow pts on P alone arm to receive L monotherapy. The primary endpoint of the study was overall survival (OS); secondary endpoints included progression-free survival (PFS), overall response rate (ORR), clinical benefit rate (CBR) and safety.
Results: The intent-to-treat and safety populations included 444 pts (N = 222/arm) and 443 pts (N = 222 in L+P; 221 in P), respectively. Baseline demographics were well-balanced between treatment groups. The most frequent adverse events (AEs) were diarrhea (L+P, 77%, Grade 3/4 20/0; P, 29% Grade 3/4, <1/<1) and neutropenia (L+P, 77% Grade 3/4, 35/16; P, 47%, Grade 3/4, 15/5). As expected, the incidence was higher in L+P; however the majority of events resolved. Of note, only 4% in L+P reported febrile neutropenia. Cardiac events were of low grade, asymptomatic, and mostly reversible. The incidence of hepatic events was similar in each arm and none met the clinical definition of Hy's Law. There were no fatal AEs in the L+P arm. OS was significantly longer in L+P compared with P alone [Cox Regression: Treatment Hazard Ratio (HR) (95% CI) = 0.64 (0.49, 0.82), $p = 0.0005$, Kaplan–Meier estimates: median OS 27.8 mos (95% CI = 23.2, 32.2) vs. 20.5 mos (95% CI = 17.9, 24.3), respectively]. Median PFS was 9.7 mos (95% CI = 9.2, 11.1) compared with 6.5 mos (95% CI = 5.5, 7.3), in the L+P vs P, respectively [HR (95% CI) = 0.52 (0.42, 0.64), stratified log rank $p < 0.0001$].
Conclusion: The combination of L+P showed a statistically significant and clinically meaningful survival advantage. Secondary endpoints support the observed clinical benefit. The combination of L+P was well tolerated.

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First-line Bevacizumab Plus Taxane-based Chemotherapy for Metastatic Breast Cancer (mBC)

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Background: Combining Bevacizumab with first-line Taxane-based chemotherapy significantly improves progression-free survival (PFS) and response rate (RR) compared with taxanes alone in HER2-negative mBC, as shown in 3 phase III trials. Until recently docetaxel and paclitaxel were registered for routine use based on those results. The aim of this retrospective study was to assess the efficacy and safety of docetaxel–bevacizumab versus paclitaxel–bevacizumab in patients (pts) with HER2-negative mBC.
Material and Method: All pts with histologically/cytologically confirmed HER2-negative mBC treated between July 2006 and March 2010 by either bevacizumab plus docetaxel, or bevacizumab plus paclitaxel were studied. Bevacizumab was continued until disease progression or unacceptable toxicity. All pts were eligible if they have not received previous cytotoxic therapy for metastatic disease. Previous hormonal therapy for mBC or cytotoxic adjuvant chemotherapy was allowed.
A search for significant factors related to the length of progression free survival (PFS) was conducted. The following variables were studied: age, hormonal receptors status, liver involvement, number of metastatic sites involved, previous exposure to taxanes containing chemotherapy in adjuvant setting.
Results: Between July 2006 and March 2010, 217 pts were treated first-line bevacizumab plus taxane-based chemotherapy for mBC.
Demographic and baseline disease characteristics of this ITT population were generally well balanced between treatment arms. Preliminary results of 86 reported a similar PFS between two treatment arms, with median values of 10 months [8−13] (HR = 1.32 [95% CI 0.81–2.17], p = 0.26). Only hormonal receptors status positive was statistically significant for PFS (HR = 0.52 [95% CI 0.32–0.85], p = 0.005).
Conclusion: In our study, we found that two treatments were similarly effective in patients with HER2-negative mBC. The safety of Bevacizumab-Taxane therapy were consistent with results from randomized first-line trials. Further details and analysis will be presented during ECCO.

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Non Basal Like Phenotype: a Potential Predictive Factor for the Effectiveness of Neoadjuvant Chemotherapy in Triple Negative Breast Cancer

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Background: Triple negative breast cancer (TNBC) negative for estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) is a distinct breast cancer subtype, which remains a great clinical challenge. TNBCs have been shown to respond to neoadjuvant chemotherapy (NAC) but it is an heterogeneous disease. In this study, we analyzed TNBC patients who were treated with NAC at Centre Jean Perrin (Clermont Ferrand, France) over a recent 9-year period to clarify the predictive factors for the effectiveness of the NAC.
Patients and Methods: Seventy TNBC patients underwent NAC with anthracyclines and taxanes from January 2002 to December 2010. Pre-therapeutical and surgical specimens were studied for expressions of ER, PgR, HER-2, epithelial growth factor receptor (EGFR), cytokeratin 5/6, Ki-67, by immunohistochemistry (IHC). We analyzed clinicopathological factors and molecular markers in regard to the response to NAC. Basal-like subtype was defined as CK5/6 positive and/or EGFR positive.
Results: The age of the patients ranged from 30 to 72 years old (median 50). The median tumour size before chemotherapy was 50 mm (range, 14–90 mm) and 40 patients had clinically positive nodes. Among the cases

56% (41 of 70) were defined as basal-like breast cancers. Tumour staging was as following: T1 (4 patients), T2 (33 patients), T3 (28 patients) and T4 (5 patients), ganglionnair staging was as following: N0 (30 patients), N1 (34 patients), N2 (6 patients). Pathological complete response (pCR) was achieved in 25 TNBC patients (35%) according to Chevallier's classification restricted to breast. According to Sataloff classification the pCR (TANA or TANB) was achived in 23 patients (32%), The pCR rate in the basal-like phenotype was signicantly lower than in the non-basal-like phenotype (14 vs 38%, respectively: $P = 0.03$). The level of expression of KI67 was not considered as predictive factors for a better response from NAC.
Conclusions: A non-basal-like phenotype was favorable factor for NAC in our study. Currently, in the absence of reliable surrogate markers or clinically available gene expression profiling, it is difficult to further define subtypes within TNBC. A minority of patients have highly chemosensitive disease with excellent outcome, however tools to prospectively identify these patients and guide chemotherapy agent selection are lacking.

5053 POSTER

Randomized Phase III Study of First-line Bevacizumab in Combination With Capecitabine or Paclitaxel for HER2-negative LR/MBC: Interim Safety Data

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Background: The ongoing CECOG-sponsored TURANDOT study (CECOG/BC.1.3.005) is investigating the efficacy of bevacizumab (Bev) + paclitaxel (P) vs Bev + capecitabine (X) in LR/MBC. Preliminary safety data from the first 167 pts [Lang, ASCO 2010] were in accordance with previously published data for these regimens. We report interim safety results after reaching the recruitment target of 560 pts.
Materials and Methods: Pts aged $\geqslant$18 years with HER2-negative, chemonaïve LR/MBC and ECOG PS 0−2 were enrolled. Prior (neo)adjuvant chemotherapy was permitted if completed $\geqslant$6 months before randomization or $\geqslant$12 months if taxane based. Pts were randomized to receive Bev+P (Bev 10 mg/kg d1, 15 + P 90 mg/m^2 d1, 8, 15, q28d) or Bev+X (Bev 15 mg/kg d1 + X 1,000 mg/m^2 bid d1−14, q21d) until PD, unacceptable toxicity or consent withdrawal. Primary objective is non-inferiority in OS with Bev+P vs Bev+X.
Results: 564 pts were randomized (Bev+P: 285, Bev+X: 279) but 3 withdrew prior to treatment (consent withdrawn/randomization failure). As of 12 January 2011, 561 pts are eligible for safety analyses (Bev+P: 284, Bev+X: 277). Median number of Bev cycles: 6.5 with P, 9.0 with X. Median age 59 years (range: 27−86). Most pts are postmenopausal (82%), ECOG PS 0 (68%), ER+ (74%). Most frequent sites of metastasis are lymph nodes and bone (54% of pts each). Overall, 39% of pts received adjuvant anthracyclines with/without taxane. Treatment-emergent AEs (TE-AEs; onset during study or within 28 days post-treatment) occurred in 91% and 89% of pts in the Bev+P and Bev+X arms, respectively, with 82% considered treatment related (Bev+P: 85%, Bev+X: 78%). Grade $\geqslant$3 TE-AEs were seen in 51% and 41% of pts, respectively, and 19% and 17%, respectively, had any serious AEs. Most frequent TE-AEs (all grades) were fatigue (Bev+P: 31%, grade 1−5, Bev+X: 23%, grade 1−3) and hand-foot syndrome (Bev+P: 2%, grade 1−2; Bev+X: 49%, grade 1−3), while diarrhea was the most frequent serious TE-AE (Bev+P: 0.4%, Bev+X: 1.4%). Overall, 22% of patients withdrew Bev/P/ X due to an AE (Bev+P: 28%, Bev+X: 15%).
Conclusions: The safety profile of Bev in combination with commonly used chemotherapy regimens for MBC in the TURANDOT study is consistent with reports from three large, phase III trials, with no new safety issues observed.

5054 POSTER

Efficacy of Biological Agents (BA) in Metastatic Triple Negative Breast Cancer (TNBC): a Systematic Review

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Background: TNBC accounts for about 15% of all invasive breast cancers, usually with an aggressive behavior and poor prognosis also because of lack of standard-of-care therapy. In this setting, BA in combination with chemotherapy (CT) may have a role, also based on TNBC cellular specific targets.
Methods: To assess the role of BA in metastatic TNBC, a systematic review of randomized controlled trials published from January 2006 to January 2011 and of communications presented at ESMO, ASCO and SABCS congresses in 2009 and 2010 was performed. Only studies comparing BA+CT versus CT alone in TNBC, or in unspecified advanced breast cancer but presenting data on TNBC subgroup, were considered. The relevant statistical variables for the pooled analysis were the log of hazard ratio (HR) and relative variance for progression-free survival (PFS) and overall survival (OS).
Results: Out of 346 Pubmed publications and 126 studies registered on http://clinicaltrial.gov/, 8 trials were selected for analysis. A total of 3463 patients were analyzed: 1286 of them were TNBC patients. BA studied were: bevacizumab (Miles 2010, Brufsky 2010 and Gray 2009), lapatinib (Finn 2009), iniparib (O'Shaughnessy 2011), sunitinib (Curigliano 2010), sorafenib (Gomez 2010) and cetuximab (Baselga 2010). A PFS improvement was detected in the group of pts receiving BA, with a relative risk reduction of 27% (95% CI: 18%-35%). I^2 statistic for quantifying heterogeneity among class of BA [1) anti-angiogenic, 2) EGFR inhibitors 3) Parp Inhibitors] was 43.8%; only class 1 and 3 showed a statistically significant improvement in PFS. No effect on OS was observed.
Conclusions: In our systematic review we detected:
1. Improvement of PFS in TNBC pts treated with BA+CT vs CT alone.
2. No single BA class showed a statistically significant superiority over others, however for EGFR inhibitors no statistically significant difference was reached.
3. The effect of BA on OS hasn't been demonstrated, similarly in the general population with non-TNBC advanced breast cancer.

5055 POSTER

The Palliative CMF is a Reasonable Salvage Treatment Option in Heavily Pretreated Patients With Metastatic Breast Cancer

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Purpose: Although cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy showed high efficacy and tolerability as adjuvant chemotherapy in breast cancer, anthracycline- and/or taxane-containing regimens have been a mainstay of adjuvant chemotherapy. Recently, many active agents, such as capcitabine, gemcitabine, and vinorelbine have improved treatment outcome in metastatic breast cancer (MBC). This study was motivated by an increasing need for effective alternative therapeutics for heavily treated MBC patients who have failed standard treatment. The aim of this study was to define the role of CMF in anthracycline and taxane pretreated MBC patients.
Material and Methods: We consecutively enrolled 44 MBC patients who underwent CMF chemotherapy with palliative intent after failure of anthracycline and taxane at Seoul National University Hospital between 2002 and 2010. The regimen of oral and intravenous CMF were administered in 25 patients (56.8%) and 19 (43.2%), respectively.
Results: Of 44 enrolled patients, median age was 50. All of patients had received prior taxane based chemotherapy, and all but one patient (97.7%) had received previous anthracycline-based chemotherapy. Forty three (97.6%), 34 (77.3%), and 36 (81.8%) were treated with fluorouracil, gemcitabine, and, vinorelbine based chemotherapy, respectively. Median 4 lines of systemic treatment were administered previously and median time to initiation of CMF chemotherapy from the diagnosis of metastasis or relapse was 20.2 months (range, 9.4–92.3 months). Median 3 cycles (range, 1−15) of CMF were administered and the relative dose intensity was 90.7%. The toxicity was mild with 11.4% of grade 2 and 18.2% of grade 3/4 neutropenia. The response rate was 15% (6/40), comprising one complete and six partial responses and disease control rate was 47.5% (19/40). The median progression free survival and overall survival were 3.3 months (95% CI, 1.3−5.2) and 9.0 months (95% CI, 6.5–11.4), respectively. The PFS of 3.5 months was better in patients with 1 to 3 metastatic sites than 1.3 months in patients with more than 3 metastatic sites. PFS and OS in triple negative breast cancer patients were not inferior to hormone positive and Her2 positive patients.
Conclusions: Palliative CMF chemotherapy is reasonable and safe as salvage treatment in heavily pretreated breast cancer patients.