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Feasibility and Toxicities Associated with PEG Doxo Versus Capecitabine as First-line Chemotherapy in Elderly Metastatic Breast Cancer (MBC) Patients; Results From the Randomized OMEGA Study of the Dutch Breast Cancer Trialists' Group (BOOG)

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Background: The absolute number of elderly women developing MBC and at some stage requiring chemotherapy is increasing. However, randomized evidence on the effectiveness and tolerability in these patients (pts) is scarce. The Dutch multicenter randomized OMEGA study compared liposomal doxorubicin (PEG doxo/Caelyx®) vs Capecitabine (Cape) as first line chemotherapy in elderly MBC pts. The current analysis focused on toxicities and feasibility of both regimens in this population.

Patients and Methods: Elderly MBC pts ($\geqslant$ 65 yrs) eligible for first-line chemotherapy were randomized between PEGdoxo (45 mg/m^2, IV, q 4 wks) or Cape (daily 2$\times$ 1000 mg/m^2, days 1−14, q 3 wks). Other eligibility criteria were: PS $\leqslant$ 3, acceptable bone marrow and liver functions, creatinine clearance $\geqslant$ 40 ml/min, adequate cardiac function. Stratification factors were PS (0−1 vs 2−3), HER2 status, visceral/non-visceral disease, adjuvant hormonal therapy (HTx), and HTx for MBC. Chemotherapy was continued for 24 weeks in the absence of progressive disease (PD) or unacceptable toxicity.

Results: Demographics of the 78 randomized pts (PEGdoxo 38, Cape 40) were: median age 75 yrs (range 65−86, 74% $\geqslant$71 yrs, 9% $\geqslant$81 yrs), median PS 1 (0/1: 77%), HER2 positive: 6.4% (unknown 19%), visceral/non-visceral MBC: 74%/26%, adjuvant HTx: 44.9%, HTx for MBC: 56.4%. Chemotherapy was administered for 24 wks in 29.5%, and discontinued due to PD in 30.8% (PEGdoxo 34%, Cape 27.5%) or intercurrent death in 5.1% (PEGdoxo: 1, Cape: 3). Chemotherapy was stopped due to toxicity/lack of benefit in 15 pts (PEGdoxo 9, Cape 6), and misinterpretation in 2 pts. Grade 3/4 toxicities (see table) were reported in 26 pts (33.3%) during 43 cycles (35%). Grade 3/4 AEs reported during $\geqslant$ 2 cycles were fatigue in 2 PEGdoxo, and 1 Cape pt (each in 2 cycles), and HFS in 2 Cape pts (in 2, and 3 cycles, resp.).

Conclusion: PEG doxo and Capecitabine are both feasible options as first-line chemotherapy for elderly MBC patients. Toxicity was acceptable, mainly being fatigue, HFS, and mucositis.

Grade 3/4 toxicity (N/% of pts)	PEG doxo	Cape
Hand Foot Syndrome (HFS)	4 (10.5%)	6 (15%)
Skin	2 (5.3%)	−
Allergy/Hypersensitivity	1 (2.6%)	−
Mucositis/stomatitis	4 (10.5%)	−
Nausea/Vomiting	−	1 (2.5%)
Diarrhoea	1 (2.6%)	1 (2.5%)
Neutropenia/Infection	2 (5.3%)	−
Fatigue	4 (10.5%)	5 (12.5%)
Cardiac events	1 (2.6%)	−
Pulmonary Embolism	−	1 (2.5%)
Neurologic symptoms	−	1 (2.5%)

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The Secondary Breast Cancer Multidisciplinary Forum (SBC- MDF): a Novel Strategy to Improve Patient Care and Allow Prospective Data Collection

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Background: Although multidisciplinary meetings take place throughout the UK, they have been designed with early breast cancer in mind. Secondary breast cancers are not routinely discussed. The management of this group of patients is often complex and the relevant support groups may not be accessed early.

There is also currently no prospective database for this population in the UK.

In South Wales, a network-wide, SBC- MDF has been running since March 2010 and is attended by clinical and medical oncologists, breast care and clinical trials nurses, radiologists and palliative care specialists. The aim of this forum is to agree a treatment plan for all new cases, and record this information prospectively, (including data on performance status, clinical trial eligibility and palliative care).

Methods: All new patients with secondary breast cancer discussed at the South Wales SBC- MDF between March 2010 and March 2011 were analysed for their presenting characteristics and the treatments they received.

Results: 139 patients with secondary breast cancer were identified, 29% stage IV at presentation. The commonest sites for metastatic disease were multiple (47%) and bone only (29%). Performance status at presentation was as follows: stage 0 − (43%), 1 − (29%), 2 − (19%), 3 − (9%). Of those with relapsed disease, 49% had undergone a mastectomy as part of their early breast cancer management, 60% had received adjuvant chemotherapy, 66% adjuvant hormones and 13% adjuvant trastuzumab. 70% of patients were ER positive, 23% ER negative, 5% unknown. 62% were HER−2 negative, 28% HER 2 positive, 9% unknown. Chemotherapy was used first line in 73 patients (52%), single agent capecitabine (16%) or docetaxel (9%) the most common regimens used. 87% of HER−2 positives received trastuzumab and 86% with bony metastases received bisphosphonates as part of their initial therapy.

Conclusions: The secondary breast cancer forum is a novel project which is coordinating the care of patients with secondary breast cancer whilst collecting invaluable statistics on this complex group. It has achieved a process of standardising treatments across a region through a panel of experts using guidelines, evidence based practice and experience.

Patients have benefitted from improved access to clinical trials and palliative medicine. Ongoing prospective studies on these patients will lead to treatment outcomes and survival data which will undoubtedly inform clinical practice.

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Retrospective Analysis of the Relative Efficacy and Toxicity of Nab-paclitaxel and Docetaxel in Metastatic Breast Cancer

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Background: Taxanes (T) are effective drugs in metastatic breast cancer. Docetaxel (D) q3 wks is associated with significant risks of febrile neutropenia (FN) and non-haematological toxicity. In 2009 nab-paclitaxel (N-P) was approved for use in place of D at our institution due to trial data demonstrating comparable efficacy but reduced toxicity. We report the efficacy and toxicity data on all patients treated with N-P in 2010 and all those treated with D in 2008 as a comparator.

Methods: Retrospective case note review of patients receiving non-trial single agent D q3 wks at any of the three recommended dose levels (60,75 or 100 mg/m^2) or N-P (all 260 mg/m^2) in 2008 and 2010 respectively. Co-administration of trastuzumab was permitted. Response rates (RR) were assessed from radiology reports in patients with measurable disease. These and toxicities were compared between D and N-P groups using Pearson chi squared tests. Progression free survival (PFS) was compared by log-rank analysis.

Results: 81 patients were identified -41 received D and 40 N-P. The groups were well balanced for ER, HER2, grade, age, prior adjuvant treatment and metastatic disease and sites of metastasis. 14 patients in each group had HER2+ tumours and received T plus trastuzumab. Ts were first line chemotherapy for MBC in 30/41 (73%) with D and 25/40 (62%) with N-P (p = 0.59). D dose was: 60 mg/m^2 in 14(34%), 75 mg/m^2 in 6(15%) and 100 mg/m^2 in 21(51%). Response was assessable in 48 patients treated with single agent T: RR was 6/25 (24%) for N-P and 14/23 (52%) for D (p = 0.004). Median number of cycles was 6 for D and N-P. Median PFS was comparable: D 203 days vs N-P 171 days (p = 0.65) although duration of follow up was significantly shorter for N-P. D induced more FN (8 vs 1 patient). Two treatment related deaths were seen with D (both FN) but none with N-P. No FN was seen when primary or secondary prophylactic GCSF was used. N-P resulted in significantly more reports of moderate-severe pain (43% N-P vs 10% D; p = 0.01) which was mostly myalgia/arthralgia and resulted in the admission of 3 patients for analgesia. Peripheral neuropathy and fatigue were comparable between groups.

Conclusions: D demonstrates a significant improvement in objective RR at the doses used in routine clinical practice compared with N-P at the licensed dose. Overall the activity and toxicity profile in this retrospective analysis favour the use of D with GCSF over N-P as single agent therapy. Updated PFS data will be presented at the meeting.

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Comparison of True Recurrence Versus New Primary: an Analysis of Ipsilateral Breast Tumor Recurrences After Breast-Conserving Therapy

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Background: Ipsilateral breast tumor recurrence (IBTR) may develop in 5−20% of early breast cancer treated with breast-conserving therapy. Some prospective and retrospective studies had propounded that two classification of IBTR, true recurrence (TR), new primary (NP), would have a different features and outcomes. This study compared survival outcomes between two patient cohorts divided clinically as either TR or NP.

Materials and Methods: Between April 1991 and December 2009, a total of 5,888 patients who diagnosed breast malignancy were treated with breast-conserving therapy in the Gangnam Severance Hospital and the Asan Medical Center. Of 5,185 patients, after excluding ductal carcinoma in situ and no available data, 74 (15 in the Gangnam, 59 in the Asan) patients (1.4 %) had pathologically confirmed IBTR. If either within the same quadrant as index tumor or below 3cm distance between index tumor and IBTR lesion and the same estrogen receptor (ER) status and the same histologic type, that was defined as TR, and the others were defined as NP. According to the this criteria, of 74 patients, 45 (60.8 %) were classified as having TR and 29 (39.2 %) as having NP.

Results: The median follow up period after initial operation was 5.8 years, 5.8 years for TR and 5.9 years for NP. The median follow up period after IBTR was 2.3 years, 2.3 years for TR and 1.6 years for NP. There were no differences in the clinicopathologic features of initial tumor between TP and NP groups except location of initial tumor, more lateral in TR (88.9 %) than in NP (62.1 %) ($p = 0.023$), more negativity of ER in TR (70.5 %) than in NP (30.8 %) ($p = 0.002$), more triple negative breast cancer (TNBC) type in TR (44.7 %) than in NP (18.2 %) ($p = 0.007$). The median time to recurrence were shorter in TR group than in NP group, but no statistically significant (2.4 years vs. 3.1 years, $p = 0.132$). There was no difference for adjuvant treatment between the two groups, but in hormonal therapy, there was a trend for the difference between NP (64.3 %) and TR (42.2 %) ($p = 0.067$). In the TR and NP cohorts, breast cancer-specific survival was 78.3 % vs. 90.4 % ($p = 0.478$), and overall survival was 75.2 % vs. 84.7 % ($p = 0.655$), respectively.

Conclusions: With the limitation of patients number, the biologic behavior of NP seems to be different with that of TR. So when we consider the treatment of IBTR, the type of recurrence should be preferentially evaluated.

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Everolimus (EVE) for Postmenopausal Women with Advanced Breast Cancer (ABC) Refractory to Letrozole or Anastrozole: Long-term Efficacy and Safety Results of the BOLERO-2 Trial

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Background: Patients with hormone-resistant ABC show constitutive activation of the PI3K/Akt/mTOR pathway. In phase II studies, the oral mTOR inhibitor EVE has shown promising efficacy when used in combination with endocrine therapy in estrogen receptor-positive (ER+) ABC progressing during treatment with nonsteroidal aromatase inhibitors. BOLERO-2 is a multinational, double-blind, placebo-controlled, phase III study comparing EVE in combination with exemestane (EXE) with EXE alone in postmenopausal women with ER+ ABC refractory to letrozole or anastrozole.

Methods: Eligible patients were randomized (2:1) to EVE 10 mg/d or placebo (PBO) in combination with EXE 25 mg/d. Stratification criteria included sensitivity to prior hormonal therapy and the presence of visceral metastases. Study drugs were continued until disease progression or unacceptable toxicity. Primary outcome was investigator assessed progression-free survival (PFS). Adverse events (AEs) were monitored continuously.

Results: 724 patients were administered EVE+EXE (n = 485) or EXE (n = 239). Median age was 62 years; 56% had visceral involvement, and 84% were sensitive to prior hormone therapy. Current analysis is based on 457 events and a median follow-up of 12.5 months. Median investigator-assessed PFS was significantly longer at 7.4 months with EVE+EXE vs 3.2 months with EXE (HR=0.44; $P < 1 \times 10^{-16}$), and by central review at 11.0 vs 4.1 months, respectively (HR=0.36; $P < 1 \times 10^{-16}$). Response rates (RR) were also improved with EVE+EXE vs EXE (12.0% vs 1.3%; $P < 0.0001$) as well as clinical benefit rate (CBR) (50.5% vs 25.5%, respectively; $P < 0.0001$). Serious AEs occurred in 26.8% in the EVE+EXE arm and 13.9% in the EXE arm, including 11.2% (EVE+EXE) and 1.7% (EXE) attributed to study treatment. The most common grade 3/4 AEs (EVE+EXE vs EXE) were stomatitis (8% vs 1%), anemia (7% vs 1%), hyperglycemia (5% vs <1%), dyspnea (4% vs 1%), fatigue (4% vs 1%), and pneumonitis (3% vs 0%). At the current time, the overall survival is still immature because of the low number of events with 17.3% for the EVE+EXE arm and 22.6% for the EXE arm.

Conclusion: EVE+EXE significantly improved PFS, RR, and CBR compared with EXE. Side effects were manageable and consistent with previous reports of EVE in this patient population. These data support the use of EVE in combination with an aromatase inhibitor as a new therapeutic option for women with hormone therapy-refractory ABC.

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Oral Combination Chemotherapy with Capecitabine and Cyclophosphamide Showed Good Efficacy and Quality of Life for Metastatic Breast Cancer Patient

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Background: Anthracyclin and taxan-containing regimens are standard for first-line chemotherapy in metastatic breast cancer (MBC). However, increasing numbers of MBC patients have experienced the use of these agents with diminishing results, leading to the need for new regimens in treating MBC.

The combination of therapy with capecitabine (Xeroda®, X) and cyclophosphamide (C) which can be given orally and which have synergic effects with no cross-resistance to anthracycline and taxans was explored. As a complete cure is difficult for MBC, it is desirable that the treatment be continued while keeping the disease stable over a long period and simultaneously promoting a high quality of life (QOL).

We estimated efficacy and QOL as affected by treatment with the XC therapy.

Material and Methods: A phase II study of the XC combination therapy was conducted in patients with MBC. Twenty-four patients with the median age 54 (range 29−77 years) were registered. A dose of 1657 mg/m^2/day of capecitabine and 65 mg/m^2/day of cyclophosphamide were given orally for 2 weeks at 3-week intervals. We evaluated the effect of treatment, adverse events and the QOL after each cycle. The QOL was evaluated by QOL-ACD, QOL-ACD-B questionnaire surveys. The full score of the questionnaire is 5.0. The primary endpoint was the response rate. Progression-free survival, adverse events and the evaluation of QOL were investigated as secondary endpoints. Remission rates were compared using the χ^2 test.

Results: The metastatic sites of these patients were the lung, liver and bone. Fourteen patients (40%) had a single metastatic site, while 10 patients had multiple sites. The median dosing period was 16.8 (4−64) cycles. A complete response (CR) was obtained in four of 24 patients (17%), partial response (PR) in 5 (21%), stable disease (SD) in 11(45%) and progress disease (PD) in 4 (17%) resulting in a clinical benefit rate of 83%. The median progression-free-survival was 12.1 months. Adverse events occurred in 85% of these patients, but all of them were grade 2 or less. The QOL survey showed 4.0 in pre-treatment and 3.4 in 4 subsequent cycles; the QOL showed no significant statistical change pre- and post-treatment.