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Safety and toxicity in Korean breast cancer patients receiving adjuvant TAC regimen chemotherapy – prospective multicenter clinical study

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Background and Purpose: More recently, a randomised phase III trial by the Breast Cancer International Research Group (BCIRG 001) has shown that the combination of docetaxel, doxorubicin, and cyclophosphamide (the TAC regimen) is superior to FAC as adjuvant chemotherapy for node-positive operable breast cancer. Unfortunately, TAC was clearly more toxic than FAC, not only with respect to neutropenic fever events, but also with respect to many extrahaematological side-effects. The aim of the study was to analyse the toxicity and tolerability of Korean breast cancer patients treated with TAC.

Materials and Methods: This study was carried out in 50 breast cancer patients who underwent primary surgery (i.e., modified radical mastectomy, skin sparing mastectomy, or breast conserving surgery) at the Department of Surgery in Soonchunhyang University (4 affiliated hospitals) from October of 2005 to March of 2007. They received a total of 260 courses consisting of TAC (75/50/500 mg/m^2 6$\times$q3wk). Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 2.0.

Results: The main toxicities were hematologic (neutropenia grade 3/4 in 100% of patients and 95.6% of cycles; febrile neutropenia in 38% of patients and 15.9% of cycles). There was no cases of septic death. The peak time of occurrence of febrile neutropenia was 7−10 days after receiving chemotherapy (mean duration; 2.12 days). Severe nonhematologic adverse events were infrequent; myalgia (30%), fatigue (22%), stomatitis (20%), nausea (16%).

Conclusion: Adjuvant chemotherapy with TAC was tolerable in Korean breast cancer patients. Although neutropenia is frequent, its consequences are manageable. The rest of the toxicity profile seems acceptable, with no significant extrahematologic toxicities, including cardiac toxicity.

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Pegfilgrastim and darbepoetin alfa as haematopoietic support for adjuvant dose dense doxorubicin + cyclophosphamide–paclitaxel in early stage breast cancer patients – results from the ACCELERATE study

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Background: Delivery of full dose chemotherapy on schedule is critical to the success of dose dense (dd) chemotherapy regimens, and granulocyte colony-stimulating factor support is recommended in this setting. Furthermore, anaemia is a common side effect of dd chemotherapy. We evaluated the feasibility of delivering a 2-weekly anthracycline–taxane regimen to breast cancer patients (pts) with pegfilgrastim and darbepoetin alfa support.

Methods: This was an Australian, multicentre, open-label study in which women with early stage node-positive or high-risk node-negative breast cancer received adjuvant doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 every 2 weeks for 4 cycles, then four 2-weekly cycles of paclitaxel 175 mg/m^2 (ddAC $\rightarrow$ T). Pegfilgrastim 6 mg was given on Day 2 of each cycle and darbepoetin alfa was administered in cycles where pts' haemoglobin was <11 g/dL. The primary endpoint was the proportion of pts with chemotherapy dose delays ($\geqslant$7 days).

Results: Between 01/2006 and 07/2007, 83 pts were treated. Mean age ($\pm$SD, years) was 46.6$\pm$9.7, 90% had Stage II−III disease, and 80% were axillary lymph node positive. In total, 664 cycles were planned, of which 656 were delivered. Eleven pts had a dose delay $\geqslant$7 days (13 cycles delayed; 2 pts >1 cycle delayed), while dose reductions were less common (Table). Most dose delays resulted from non-haematological toxicity (mainly fever/infection, 3 patients). There were few grade 3−4 haematological toxicities; febrile neutropenia occurred in 4 pts (5%), 2 of whom required a dose reduction. Darbepoetin alfa was given to 54 pts (65%); only 1 pt (1%) received a red blood cell transfusion.

Endpoints	Pts (N = 83), n (%)
$\geqslant$1 dose delay ($\geqslant$7 days)	11 (13)
Due to:	
Non-haem toxicity	9 (11)
Haem toxicity	1 (1)
Pt request	1 (1)
$\geqslant$25% dose reduction	5 (6)
Due to:	
Febrile neutropenia	2 (2)
Other haem toxicity	1 (1)
Non-haem toxicity	2 (2)
Grade 3−4 toxicity overall	38 (46)
Grade 3−4 events in $\geqslant$5% of pts:	
Infections	7 (8)
Myalgia	7 (8)
Febrile neutropenia	4 (5)
Fatigue	4 (5)
Peripheral neuropathy	4 (5)
Nausea	4 (5)

Haem = haematological.

Conclusions: In this study, delivery of ddAC $\rightarrow$ T was feasible with pegfilgrastim and darbepoetin alfa support. There were minimal dose delays $\geqslant$7 days due to haematological toxicity (1/14, 7%) and just 1 transfusion. In CALGB9741, where pts received ddAC $\rightarrow$ T with 7 days of filgrastim and no erythropoietin support, 15% had a dose delay (any duration) due to haematological toxicity and 13% of pts required a blood transfusion.

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Aromatase inhibitor as neoadjuvant hormone therapy for breast cancer

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Background: Aromatase inhibitors block estrogen biosynthesis systemically or in cancer tissues, and are increasingly used to treat postmenopausal women with breast cancer. Here we report the efficacy of aromatase inhibitors and the effect on the expression of hormone receptors and Ki67 in breast cancer tissue.

Methods: 17 postmenopausal patients with operable or locally advanced estrogen receptor (ER) positive breast cancers were treated with anastrozole or exemestane. Biopsies were obtained pre and post treatment and assessed by immunohistchemistry (IHC) for Ki67, ER and progesterone receptor (PgR). Allred IHC score were assigned and categorized as low (0−2), medium (3−5) and high (6−8).

Results: The clinical objective response rate was 70.6%, without progression. Twelve of 17 patients showed partial response (PR) and 5 showed no change (NC). An increased in PgR category in 1 of 12 responding tumors. A decrease in PgR category was more frequent in responding tumors (9 tumours [75%] PR vs. 3 tumors [60%] NC). Percentage change in Ki67 expression from baseline during treatment is 20.4$\pm$13.6% in responding tumors and 138.6$\pm$92.0% in non-responding tumors, respectively. Suppression of the proliferation marker Ki67 was greater in responding tumors than in non-responding tumors.

Conclusion: Neoadjuvant aromatase inhibitor provided satisfactory efficacy and safety profiles in breast cancer. The main biological effects consisted of a reduction in PgR expression for responders and a decrease in Ki67 expression.

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The benefit using an integrated electronical study platform for a presurgical therapy trial (HEDON) in primary breast cancer

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Background: Normally, the capture of clinical trial data is labor intensive and error-prone, requiring data to be transcribed into a paper case report

form (pCRF) or, more recently, entered manually into an electronical data capture systems (EDC).

Method: In 2005 a collaboration between researchers of the Dept.OBST&GYN TUMunich and Siemens Medical Solutions developed a method of electronically transferring clinical data gathered at the point of care for use in prospective clinical trials. This single-sign-on patient aware electronic platform for clinical trials has been validated in its whole and is prepared to support the regulatory requirements as specified by FDA's 21 CFR part 11 compliance.

Enabling immediate data transfer, the solution is being tested in a pilot study, the HEDON trial (Trastuzumab-Docetaxel-Neoadjuvant), an investigator initiated phase II trial concerning primary systemic therapy of breast cancer and its translational research part (TransHEDON) evaluating therapy response markers as an essential component of this trial. Both started in February 2006 and are ongoing.

To quantify the benefits of our platform, an integrated evaluation project was performed. For a pre-defined time period, data capture and data management processes were performed paper based and electronically. This allows thorough and critical analysis of all involved processes.

Results: The evaluation project proved that the use of such an integrated electronical platform significantly improves efficiency and enables real-time data availability for clinical trial sites.

Conclusion: This innovative solution offers a scalable, automatic transfer of data between a hospital information system (HIS) and an electronic data capture (EDC) system, overcoming interoperability challenges associated with systems that operate on different technical standards and work within distinct business environments.We consider this integrated system to bevery helpful for implementation of clinical trials into a routine hospital setting. This will increase motivation and enhance the quality of studies.

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The experience of capecitabine using in neoadjuvant polychemotherapy for breast cancer treatment II–III stages

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Background: Capecitabine is an oral prodrug that is converted to its only active metabolite, FU, by thymidine phosphorylase. It has been successfully proved in treatment of metastatic breast and locally advanced BC. At present the usage of capecitabine in an operable BC treatment has not been investigated enough.

Material and Methods: 78 primarily-revealed patients with II–III stages of BC (T1−3 N0−2M0), aged from 39 to 68, were enrolled. 1 group – 38 patients were treated with scheme CMC: capecitabine (2000 mg/m^2 on days 1−14 per os), cyclophosphan (200 mg/m^2 on days 1−14 i.m.), metotreksat (40 mg/m^2 on days 1 and 8 i.v.), with 14-day interval between cycles. In total the patients received 87 cycles. 2-nd group – 40 patients were treated with scheme CAC: capecitabine (2000 mg/m^2 on days 1−14), cyclophosphan (200 mg/m^2 – day 1−14 i.m.), and adriamicyn (30 mg/m^2 on days 1 and 8 i.v.), with 4-week interval between cycles. In total 110 cycles. All the patients (from two groups) were received to 2−4 cycles of chemotherapy in condition of the dispensaries. The direct efficiency was estimated on scale RESIST, toxicity – on CTC-NCIC.

Results: efficiency on the sum of full and partial regresses was: for group CMC – 68.3%, total regress – 5.3% (2), full morphological regress – 1 case, partial regress – 63.2% (24). Stabilization of process was registered in 28.9% (11) supervision, while progress was noted in 2.6% (1). In group CAC the direct efficiency was: 75%, total regression – 10% (4), full morphological regress in 2 cases, partial regress – 65% (26). The effect received allowed to hold conservative surgery in 50% (CMC) and 47.5% (CAC). The results of treatment were relatively satisfactory. The main difficulties were: a nausea/vomiting (1−2 grade) – 55% (CMC) and 46.4% (CAC); a stomatitis (2 grade) – 17.2% (CMC) and 21.8% (CAC); leukopenia (1−2 grade) – 43.6% (CMC) and 40% (CAC); leukopenia (2 grade) – 2.3% (CMC) and 1.8% (CAC); enteritis (2 grade) 1.1% (CMC); leukopenia (3 grade) – 11.4% (CMC) and 9% (CAC). During treatment the influences of chemotherapy on cardiovascular system was not registered.

Conclusions: The usage of neoadjuvant polychemotherapy under schemes SMH and SAH is satisfactory and effective treatment which enables to increase quantity conservative surgery operations of patients with II−III BC stages.

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Antitumor properties of bisphosphonates and possible prevention of bone metastases in breast cancer

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Background: Developing bone metastases (mets) is a devastating event for patients (pts) with breast cancer (BC), placing them at risk for potentially debilitating skeletal-related events (SREs). Bisphosphonates (BPs) have established efficacy for the prevention of SREs in pts with bone mets; preclinical and preliminary clinical data suggest possible antitumor effects of BPs and potential bone mets prevention.

Material and Methods: Data from recent publications and congress presentations were compiled and evaluated, and the status of ongoing clinical trials of BPs for the prevention of bone mets from BC was reviewed.

Results: Initially, antitumor effects of zoledronic acid (ZOL) were identified in preclinical studies. ZOL inhibits tumor cell viability and impedes invasion and adhesion of human BC cell lines to soft tissues and bone. ZOL also acts synergistically with chemotherapy (Cx) agents in animal models. ZOL in combination with doxorubicin increased apoptosis in human BC cell lines in vitro and inhibited tumor growth in a mouse xenograft model of human BC. Recent clinical evidence also suggests that ZOL may have antitumor effects. Low-dose ZOL in cancer pts with bone mets reduced serum levels of VEG-F ($P < 0.04$) suggesting an inhibitory effect on angiogenic signaling. In BC pts without evidence of distant mets (N = 172), ZOL administration for 6 mo appeared to reduce the frequency of isolated tumor cells in bone marrow vs pts who did not receive ZOL (13% vs 27%). Furthermore, results from the large, prospective Z-FAST and ZO-FAST trials of ZOL for the prevention of aromatase-inhibitor associated bone loss indicate a trend toward lower disease recurrence in BC pts receiving upfront ZOL vs the delayed group. Several clinical trials are investigating the efficacy of BPs for the prevention of bone mets in BC pts (NSABP-B-34, AZURE, SUCCESS, S0307). The AZURE study will assess the effect of ZOL in combination with adjuvant Cx and/or endocrine therapy on disease-free and bone-mets-free survival in women with stage II/III BC. Preliminary safety data indicate that ZOL does not compromise delivery or dose intensity of adjuvant Cx nor increase the frequency of adverse events. An interim analysis of AZURE will be performed in 2008.

Conclusions: Preclinical and preliminary clinical studies suggest that BPs could potentially prevent or delay development of bone mets in pts with BC. Several large, randomized trials are ongoing to evaluate BPs in this setting.

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Fine-needle aspiration cytology for the evaluation of palpable axillary lymph nodes before sentinel node biopsy in patients with breast cancer

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Background: Sentinel lymph node biopsy (SLNB) has now been accepted as standard for staging breast cancer with clinically negative axillary lymph nodes (ALN). However, with the high incidence of ALNs metastases, patients with palpable ALNs could avoid SLNB if the ALNs metastases were detected before SLNB. The aims of this study were to evaluate the value of preoperative fine-needle aspiration cytology (FNAC) of palpable ALN in patients with breast cancer.

Material and Methods: Between Oct. 2004 and Dec. 2007, preoperative FNAC of palpable ALNs was performed in 143 pts. SLNB was performed in patients with negative ALNs FNAC, and ALND for patients with positive ALNs FNAC. ALNs cytological diagnoses were compared with the final axillary pathological outcomes. The sensitivity, specificity, accuracy, negative predictive value and positive predictive value of palpable ALNs FNAC were analyzed.

Results: Among the 143 pts, 86 (60.1%) were positive for ALNs according to both the FNAC and pathology. In 29 pts (20.3%), both were negative. In 28 pts (19.6%), the FNAC was negative, but metastases were found in the final pathology. Overall, the sensitivity, specificity, accuracy, positive predictive value and negative predictive value of FNA were 75.4%, 100%, 80.4%, 100%, and 50.9%, respectively. ALNs metastases could accurately diagnosed with FNAC in 75.4% pts (86/114), and SLNB could be avoided. Nearly half (28/57, 49.1%) of the patients with clinical palpable axillary nodes and negative FNAC had no metastases in the ALNs, and ALND could be avoided with SLNB. The sensitivity for clinical N1 (n = 118), N2 (n = 23) and N3 (n = 2) were 68.9%, 100% and 100%, respectively. The sensitivity for T1 (n = 7), T2 (n = 122), T3 (n = 4) and T4 (n = 11) were 83.3%, 70.2%, 100% and 100%, respectively. The sensitivity for IIa (n = 5), IIb (n = 110), IIIa (n = 17) and IIIb (n = 11) were 75%, 67.5%, 100% and 100%, respectively.