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Tolerability of lapatinib in combination with taxanes (T) in 507 patients with breast cancer (BC)

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Background: This analysis presents tolerability data for combination of Lapatinib (Tyverb®/Tykerb®) (L), an oral, dual ErbB1/B2 tyrosine kinase inhibitor and taxanes (T), the most frequently used cytotoxic in BC treatment. The side-effects observed with EGFR inhibitors (erlotinib, gefitinib) in combination with T were neutropenia, diarrhea and rash. Data from a range of clinical studies with L and paclitaxel (P) or docetaxel (D) are presented.

Methods: Pharmacokinetics (PK) and preliminary safety data from 507 patients are summarised.

Results: PK analysis from study EGF10009 (q3w), show systemic exposure was increased for both L (21%) and P (23%) at doses of 1500 mg daily and 175 mg/m^2/q3w, respectively. PK analysis from study EGF10021, (L 1250 mg & D 75 mg/m^2 with prophylactic pegfilgrastim) indicated no significant effect on systemic exposure of either agent.

Toxicities $\geqslant$ grade 3, across all studies for all patients include, neutropenia (15%), diarrhea (18%), rash (5%), febrile neutropenia (3%), neuropathy (4%), and LVEF decrease (0.6%). The rate of neutropenia, rash and neuropathy were similar in combination to each agent alone, however diarrhea was more common. The frequency and severity of diarrhea was increased in studies EGF10009 and EGF102580 where no proactive treatment of diarrhea was introduced, whereas in study EGF105764, with proactive treatment, a lower incidence of $\geqslant$grade 3 diarrhea was reported (5%). For study EGF30001 and the overall diarrhea in this pooled analysis, the $\geqslant$ grade 3 diarrhea observed is similar to what is seen with lapatinib monotherapy clinical studies. The incidence of $\geqslant$ grade 3 LVEF decrease was low (0.6%) compared with reports of docetaxel plus trastuzumab (TRZ) combinations.

Conclusions: T plus L combinations have significant activity in HER2+ BC (60−70% RR reported in EGF102580 and EGF30001) and have a predictable and manageable safety profile. Proactive diarrhea management is essential for these combinations and dose adjustments should be considered in patients with persistent or severe diarrhea.

Study	Phase/L+T	Dose L mg/d T mg/m^2	Tumor	N	Diarrhea $\geqslant$G3 (%)
EGF10009	I/L+P	1250–1500/135–225 q3w	Refractory	44	7
EGF10009	I/L+P	1500/80 qw	Refractory	12	50
EGF105764	II/L+P	1500/80 qw	1L MBC	57	5
EGF102580	II/L+P	1500/80 qw	IBC	49	61
EGF10021	I/L+D	1000–1500/50−75 q3w	Refractory	52	10
EGF30001	III/L+P	1500/175 q3w	1L MBC	293	15

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Severe skin toxicity observed in patients (pts) treated with capecitabine (CAP) and weekly paclitaxel (PACLI) for metastatic breast cancer (MBC)

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Introduction: Skin toxicity has recently been recognized as an important toxicity of antineoplastic drugs. We report the incidence of skin toxicity in MBC treated with innovative regimen of CAP and weekly PACLI.

Patients and Methods: Eleven MBC patients were included into phase I study with the combination of CAP 2000 mg/m^2 daily (DI−D14) and escalating doses (60 mg/m^2, 75 mg/m^2 and 90 mg/m^2) of weekly PACLI (DI, D8, D15) and 15 MBC patients proceeded into phase II study of CAP 2000 mg/m^2 daily (DI−D14) combined with weekly administered PACLI 60 mg/m^2 (DI and D8). Regimens were repeated every 3 weeks. Adverse events were graded according to Common Terminology Criteria for Adverse Events, version 3.0.

Results: All 26 patients were evaluable for toxicity. Two patients in phase I receiving PACLI 75 mg/m^2 in combination with CAP experienced grade 3 nail toxicity, with grade 3 hand-foot syndrome (HFS) in one patient and grade 2 dermatitis in the other, which were deemed as dose-limited toxicity. Based on this, weekly PACLI dose of 60 mg/m^2, was selected for phase II study. The total of 18 patients received CAP 2000 mg/m^2 daily (DI−D14) and 60 mg/m^2 weekly PACLI combination. Toxicity of this regimen was mild without grade 3/4 adverse events. Skin toxicity was as follows: grade 1/2 HFS in 11/18 pts, grade 1/2 rash/desquamation in 8/18 pts and grade 1/2 nail toxicity in 4/18 pts. Due to repeat grade 2 HFS, despite CAP dose reduction, 1/18 pts went off therapy.

Conclusion: According to our findings the combination of CAP 2000 mg/m^2 daily (DI−DI4) and with weekly PACLI 75 mg/m^2 is not feasible due to severe skin toxicity.

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Effects of chemotherapy on olfactory function in breast cancer patients

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Background: Disorders of olfaction have a negative impact on quality of life and nutrition and are frequent complaints in patients undergoing chemotherapy. This prospective study investigates the olfactory function of breast cancer patients receiving chemotherapy.

Material and Methods: The olfactory function was tested 4 times in 63 previously chemo-naïve breast cancer patients: Before, in the midth, directly after, and 3 months after chemotherapy. Olfactory testing was performed by means of "Sniffin' Sticks", a validated instrument containing separate tests for odor tresholds, odor discrimination, and odor identification. Seven patients received Carboplatin, 56 patients received combination chemotherapy consisting of 5-Fluorouracil, Epirubicin, Cyclophosphamid, or Docetaxel and Adriamycin. The data were analyzed using the variance analysis.

Results: During chemotherapy, the olfactory function decreased. Three months after chemotherapy, the olfactory function recovered almost back to baseline. This change was significant for the score of odor thresholds (8.5$\pm$2.3 – 6.5$\pm$1.9 – 4.9$\pm$1.5 – 7.5$\pm$1.9), odor discrimination (13.8$\pm$1.9 – 12.4$\pm$1.9 – 11.6$\pm$2.2 – 13.7$\pm$1.5), and odor identification (14.3$\pm$1.9 – 13.8$\pm$1.9 – 13.3$\pm$2.2 – 14.1$\pm$1.8). There was no significant difference between patients receiving Carboplatin or any other chemotherapy.

Conclusions: Chemotherapies in patients suffering from breast cancer have a significant effect on olfactory function. Odor threshold is reduced more than odor discrimination and odor identification. Reduced olfactory function is one reason of reduced appetite leading to lower energy intake and weight loss during chemotherapy. Additional flavoring during chemotherapy may compensate the diminished chemosensory function, reduce weight loss and thus improve quality of life of breast cancer patients.

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Clinical characteristics of bone fractures in breast cancer women receiving adjuvant aromatase inhibitors

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Background: The evidence exists that non-steroidal aromatase inhibitors (AI) therapies used in adjuvant setting carry an increased risk of bone fractures. Before the clinical value of preventive measures for that events (such as bisphosphonates, life-style changes, etc.) will be clearly established, the careful identification of patients' subgroup with the highest fracture risk might be helpful in making decision regarding the most optimal sequence of endocrine therapy and supportive care.

Material and Methods: Data on skeletal adverse events and predictive factors of fracture risk were collected during the questionnaire-based interview from 96% patients treated with adjuvant AI in three separate institutions between 01.01.2002 – 31.12.2007. Adjuvant anastrozole (N = 288) or letrozole (N = 43) was given to 331 postmenopausal breast

cancer women as primary therapy (N = 160) or in sequence to previous tamoxifen (N = 171) for a median period of 54 months (range: 7.5−87).

Results: Nineteen cases (5.74%) of minimal trauma fractures were identified after 9−47 (median: 25) months of anastrozole administration (median duration of AI medication in group without fractures: 31 months, range: 7.5−87; difference not significant); women who took letrozole did not experience any bone fractures. Patients who experienced bone fractures under IA were significantly younger that those without that complications (median: 47 vs. 60 years; $p = 0.01$) and more frequently subjected to surgical/radiological menopause (57.89% vs. 3.85%; $p < 0.001$). None of cases with bone fractures was pretreated with tamoxifen before AI therapy was started in contrast to those without bone fractures (tamoxifen for at least 6 months: 0% vs. 59.21%, respectively; $p < 0.05$). No statistically significant differences were observed between two study subgroups in terms of frequency and regimen of anticancer chemotherapy as well as risk factors for bone fracture, such as: initial body mass index, previously diagnosed osteoporosis/osteopenia, life-style (physical activity, cigarette smoking, alcohol abuse, diary products intake, calcium supplementation), parental history of osteoporosis/hip fracture/multiple bone fractures, co-morbidities and medications related to bone mass changes (including hormone replacement therapy), pretreatment history of minimal trauma fractures. Relatively low rate of bone fractures did not allow to perform the multivariate analysis.

Discussion: Results obtained in this preliminary study: 1) revealed that traditionally used osteoporosis fracture risk factors do not reflect the probability of AI therapy associated bone events properly, thus suggest difference between AI induced bone loss and that observed after menopause; 2) support the osteoprotective activity of tamoxifen; 3) indicates that AI-related bone fractures in unselected group of breast cancer women are less prevalent than what has been described in clinical trials.

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Some aspects of scalp cooling in breast cancer patients receiving chemotherapy

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Background: Alopecia, hair loss, is a common and distressing side effect of chemotherapy. Hair loss stigmatises by making cancer visible. Scalp cooling is worthwhile supportive care that is applied in breast cancer patients with chemotherapy schedules that cause (severe) hair loss. In 2008 scalp cooling is practised extensively in the UK and the Netherlands, but among others also in Belgium, Ireland, Norway, Sweden and Switzerland.

Methods: In 2005 a PhD-project has started comprising studies related to scalp cooling in breast cancer patients. 1. In order to optimise cooling methods the impact of post-infusion cooling times on the preservation of hair was determined in the 3-weekly docetaxel and FEC-high dose (epirubicine 90 mg/m^2 or more) regimens. Initially the post-infusion cooling times were 90 minutes. Now patients are randomised between post-infusion cooling times of 45 and 90 minutes in docetaxel and 90 and 150 minutes in FEC-high. 2. Impact of hair loss on well being and body image was measured by questionnaires completed before starting chemotherapy, 3 weeks and 6 months after the last chemotherapy session. Scalp cooled patients were compared to non-cooled patients 3. The risk of (scalp) skin metastases has been studied in the Munich Cancer Registry in non-cooled patients without metastases at diagnosis (n = 28.916). Furthermore medical records research was performed among all Dutch scalp cooled patients (n = 395) from 1997 to 2005.

Results: Results of our studies show: 1. 53% of 250 patients treated with FEC high dose and 82% of 38 patients treated with docetaxel did not require a wig after chemotherapy with 90 minutes post-cooling. Results of scalp cooling in randomised patients are not known yet, data will be presented at EBCC conference. 2. higher well being and better body image in successfully scalp cooled patients (n = 32) than in patients not receiving cooling (n = 142) who in turn have better results than not-successfully cooled patients (n = 30). 3. 694 (11%) of 6205 patients with metastases in follow up presented with skin metastases. Skin metastases alone comprised 150 patients (2.4%). While about 80% of skin metastases present on the trunk, the percentage of scalp skin metastases will be lower than 0.5%. Medical record research showed 2 patients with scalp skin metastases, these patients were treated with chemotherapy in the palliative setting.

Conclusion: More than half of the patients do not require a wig in two chemotherapy schedules that normally induce severe hair loss. Preservation of hair by scalp cooling leads to a better well being and body image. Hazards of development of scalp skin metastases by scalp cooling seem very low, but can not be excluded unequivocally.

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Electrolyte abnormalities and side effects of zoledronate in patients with bone metastases

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Background: Zoledronate is generally used for the treatment of bone metastases from different kind of neoplasms. Hypocalcemia and elevation of serum creatinine are expected adverse events during this therapy, although their actual incidence is unknown. The use of serum calcium and creatinine is therefore recommended. The primary aim of this study was to establish the actual incidence of hypocalcemia and elevation of serum creatinine during treatment with zoledronic acid. Skeletal-related events (SREs) and side effects were also assessed.

Materials and Methods: Serum creatinine and calcium levels were evaluated in 240 consecutive patients (83 males, 157 females, mean age 59.8 years) with metastatic bone lesions from different solid tumors, treated with zoledronic acid.

Results: Overall, 95/240 patients (39.6%) developed hypocalcemia: G1 in 47 patients (49.5%), G2 in 37 (38.9%) and G3 in 11 (11.6%). Median time-to-occurrence of hypocalcemia (any grade) was 2 months (range 0−35). A higher grade of hypocalcemia was associated with earlier appearance ($p = 0.0001$). Increased serum creatinine was observed in 33/240 patients (13.7%), of whom 19 had G1 (57.6%), 11 had G2 (33.4%) and 3 had G3 (9%). Median time-to-serum creatinine increase (for any grade) was 5 months (range 0−29). Elevated levels of creatinine were associated with advanced age ($p = 0.0017$).

Conclusions: The reported high incidence of serum hypocalcemia and creatinine strongly supports the need for accurate monitoring of plasma calcium and creatinine levels.

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Radiogrametrical analysis of clavicle structure – predictive factor for bone fractures in breast cancer women treated with adjuvant anastrozole?

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Background: Adjuvant anastrozole (ANS) therapy increases bone fractures risk in postmenopausal breast cancer (BC) women. Some studies showed the bone mineral density has low sensitivity to assess bone fracture risk (BFR) in general population and seems to be even less predictive in BC women treated with aromatase inhibitors. Some data suggests that other than densitometric features of bone ("bone quantity"), such as bone geometry, microstructure ("bone quality") may contribute to BFR. We studied the influence of adjuvant ANS on radiological features of bone structure and its predictive value in estimating BFR.

Patients and Methods: Data for the study were collected from 85 BC women: 48 taking adjuvant ANS as a primary endocrine therapy and non-randomelly matched group of 37 patients who received no further endocrine treatment following adjuvant chemo-/radiotherapy. The influence of ANS on bone was assessed using the radiogrametrical digital analysis of clavicle and II. rib based on chest PA X-ray radiograms routinely taken in each patient before and min. 6 months of treatment/observation afterwards (median: 16, range: 6−45 mts / 17, range: 6−43 mts, respectively) and then digitally processed using image analyzer.

Results: 1) The comparative analysis of the pairs of data taken before and during treatment revealed that the linear spongious/cortical width ratio (S/C) increases significantly in patients being under ANS in both evaluated skeletal locations (clavicle $p < 0.001$; II. rib $p < 0.01$), whereas patients from control group experienced only statistically not significant increase of the S/C ratio; 2) typical feature observed in ANS-treated patients and control cases was the increase of the contrast between cortical and spongious part of bone shadow in clavicle and II. rib (parameter C), however the difference did not reach significance; 3) comparison of changes in bone structure during treatment/observation period showed the significantly