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Characteristics of patients with long-term survival after occurrence of liver metastases from breast cancer

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Background: The occurrence of liver metastases in metastatic breast cancer is related to a significant impairment of prognosis with a median survival between 15 and 19 months. It was the aim of our study to define prognostic parameters for patients with liver metastases, especially to characterize those patients with long-term survival.

Material and Methods: We studied retrospectively n=350 patients with liver metastases from breast cancer. All patients were stratified following the survival after first occurrence of liver metastases in steps of <12 months, 12-24 months, 24-36 months and >36 months. All subgroups were analyzed regarding clinical, histopathological and therapeutic parameters.

Results: Median survival after occurrence of liver metastases was 20 months, n=66 patients survived longer than 36 months after primary diagnosis of hepatic metastases. Patients with long-term survival were in median younger at age at the time of primary diagnosis of breast cancer as well as at occurrence of liver metastases, compared to all other studied patients (42 years rsp. 45 years versus 48 years rsp. 52 years, p<0,01). None of the patients with long-term survival had ascites at primary diagnosis, 8% showed a hepatomegaly and only 5% were icteric. Liver enzymes were not elevated in 65% and tumor markers only in 61% compared to 76% within all other patients.

Patients with long-term survival showed more often a limited number of metastases (d5) than all other studied patients (52% versus 32%). No differences were found regarding the histological tumor type and the rate of nodal negative patients, ER and PR were positive in 68% and 67% of the patients with long-term survival compared to 54% and 46% of all other studied patients, there were no major differences in HER2-expression, an expression of Ki-67 of > 40% was less often detected in those patients with long-term survival than in all other patients (26% versus 42%).

Conclusions: Younger patients with limited liver metastases without clinical signs of hepatic affection and certain favourable clinical and histopathological pattern seem to have a better prognosis and may be better long-term responsive to multimodal tumor therapy.

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Quality of life (QoL) in patients with metastatic breast cancer (MBC) treated with capecitabine (Xeloda)

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Background: When choosing appropriate therapy for patients with MBC it is important to consider the QoL benefits of oral treatments, such as the novel fluoropyrimidine capecitabine (Xeloda®).

Patients and Methods: QoL in women receiving oral capecitabine as second- or third-line therapy for MBC was assessed at baseline, before the first cycle of treatment, at weeks 7 and 13, and at the end of treatment using the EORTC QLQ C-30 questionnaire and the specific model for breast cancer (BR-23). The proportion of patients with an improvement, stabilisation or worsening of QoL scores was determined from week 7 onwards and analysed using generalised linear models for repeated measures. The generalised estimating questions technique and an SAS programme (system version 8.2) were used for the statistical analysis.

Results: 331 patients were evaluated: mean age, 51.1 years (range 28.072.0 years); white/Caucasian (86.7%). Almost 50% of patients completed the questionnaires at all time points. Significant improvements in the following QoL variables were detected: global health status (p<0.0001), role functioning (p<0.0001), emotional functioning (p<0.0001), fatigue (p=0.0006), nausea/vomiting (p=0.007), pain (p<0.0001), insomnia (p=0.001), appetite loss (p=0.0001), constipation (p<0.0001), financial problems (p=0.0004), body image (p=0.0002), future perspective (p<0.0001), breast symptoms (p=0.0003), arm symptoms (p=0.003), sexual enjoyment (p=0.02) and hair loss (p=0.0002). Despite a small worsening of diarrhoea symptoms up to week 7, this was not observed over the whole study. The proportion of patients remaining stable or improving was between 70 and 80% for most scales. At least 30% of patients reported improvements in the following QoL scales from week 7 onwards: pain (41%); fatigue (39%); emotional functioning (37%); future perspective (37%); arm symptoms (35%); role functioning (34%); hair loss (34%); global health status (33%); cognitive functioning (31%). At the end of treatment, 44% of patients showed an improvement in global health status and 26% had stable scores (QLQ-C30 scale).

Conclusion: In light of its proven efficacy, safety and convenience, treatment with capecitabine has a direct impact on patients' QoL. This important outcome should be considered alongside well-established measures of treatment response (objective response, time to disease progression and overall survival) in patients with MBC.

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Capecitabine and taxanes: combination versus sequential therapy in anthracycline-pretreated metastatic breast cancer (MBC): findings from the Mexican Oncology Study Group (MOSG) phase III trial

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Background: As docetaxel (T), paclitaxel (P) and capecitabine (X) have proven activity, different toxicity profiles and in vitro synergism, they are ideal combination partners for MBC. However, the optimal regimen/schedule has yet to be defined. The aim of this study was to compare the efficacy of sequential X-taxane, XT or XP combination regimens.

Methods: 219 patients with anthracycline-pretreated MBC have been recruited and randomized to receive 3-weekly cycles of X 1,250 mg/m^2 bid days 114, followed after progression by T 100 mg/m^2 or P 175 mg/m^2 day 1 (arm A), X 825 mg/m^2 bid days 114 plus P 175 mg/m^2 day 1 (arm B) or T 75 mg/m^2 day 1 (arm C). With the exception of the proportion having lung metastasis (A, 16%; B, 29%; C, 46%, p=0.003), patient characteristics were similar in each arm.

Results: Response rates in the 177 evaluable patients in arms A, B and C were: CR (29.6% vs 35.4% vs 37.9%); PR (25.9% vs 27.7% vs 34.5%) (A vs C arms OR, p=0.06); SD (11.1% vs 9.2% vs 8.6%). The disease-free period between the end of anthracycline treatment and the start of the trial was predictive for response: <6 months (33% vs 56% vs 69%); >36 months (71% vs 67% vs 91%). Progression-free survival (PFS) was 55% vs 67% vs 71% (A vs C arms, p=0.059) at 6 months and 39% vs 59% vs 59% (p=ns) at 12 months. Overall survival (OS) at 6 and 12 months was: 91% vs 96% vs 86% and 78% vs 80% vs 71%, respectively (both p=ns). Following X monotherapy in arm A, 28/57 evaluable patients had progression (either from the start of the trial or after PR or SD): 43% received T, 11% P, 14% radiotherapy/hormonal therapy and 32% received no further treatment because of rapid tumor progression or patient refusal. Grade 3-4 toxicity for 291, 348 and 342 delivered cycles per arm was: HFS 5.5% vs 3.8% vs 3.6%; mucositis 2% vs 2.1% vs 1.8%; diarrhea 1.8% vs 2.6% vs 1.1%; neutropenia 0.3% vs 0.6% vs 0.3%.

Conclusions: The results indicate a trend towards a higher response rate and PFS with combination treatment, particularly XT compared with sequential X-taxane, although OS was similar in all groups. Because only half of the patients in arm A continued with a taxane following X, X-based combination rather than sequential therapy seems reasonable to be considered upfront. Trial is still ongoing and updated OR, PFS, OS plus quality of life results will be presented during the meeting.

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Alleviation of bone pain with oral and intravenous ibandronate in women with metastatic breast cancer

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Background: Up to 80% of patients with advanced breast cancer will go on to present with or develop metastatic bone disease (MBD). Many patients experience severe bone pain, with detrimental effects on patient mobility and quality of life. Alleviation of bone pain is therefore an important aspect of MBD management. The effect on bone pain of ibandronate, a new, highly-potent, third-generation bisphosphonate, has been investigated in phase III trials of patients with MBD from breast cancer.

Methods: Three international, multicenter, randomized, double-blind, placebo-controlled trials over a 96-week treatment period were conducted. In a trial of intravenous (i.v.) ibandronate, patients were randomized to receive i.v. ibandronate 6mg (n=154) or placebo (n=158), infused over 12 hours every 34 weeks. In two trials of oral ibandronate, patients received a 50mg daily dose (n=287) or placebo (n=277). Pooled data from the oral trials were analysed for efficacy. Patients were required to report their level of bone pain on a 7-point scale (from 0=none to 6=requiring >100mg/day morphine or equivalent) . Quality of life (QoL) was also evaluated using the EORTC QLQ-C30, a 30-item questionnaire that produces QoL scores for global health status and five functional domains.

Results: Patients receiving i.v. ibandronate 6mg or oral ibandronate 50mg experienced a rapid initial reduction in bone pain score that remained below baseline levels over 2 years of treatment. The mean reduction in baseline bone pain score with i.v. ibandronate 6mg was 0.28, compared with an increase of +0.21 with placebo ($p<0.001$). In the pooled oral studies, oral ibandronate 50mg reduced mean baseline bone pain scores by 0.10, compared with an increase of +0.20 with placebo (p=0.001). Analgesic use scores were also significantly lower with oral ibandronate 50mg compared with placebo (p=0.019). Pain reductions with i.v. ibandronate 6mg and oral ibandronate 50mg were accompanied by significant improvements in global QoL compared with placebo (p=0.004 and p=0.03, respectively). Ibandronate 6mg i.v. significantly improved functional domain scores for physical function (p=0.034), emotional function (p=0.025) and social function (p=0.008), while oral ibandronate 50mg significantly improved physical function ($p<0.05$) and role function ($p<0.01$) domain scores compared with placebo.

Conclusions: Treatment with i.v. ibandronate 6mg and oral ibandronate 50mg relieves bone pain in patients with MBD from breast cancer. Unlike other bisphosphonates for MBD, pain reductions with oral and i.v. ibandronate are maintained below baseline levels over 2 years of treatment, and are accompanied by significant improvements in QoL.

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Capecitabine monotherapy is active, well tolerated and provides convenient outpatient therapy for patients with taxane-pretreated advanced breast cancer: findings from an expanded access program

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Background: Phase II/III trials have shown the oral fluoropyrimidine capecitabine (Xeloda®) to be active and well tolerated in patients with advanced breast cancer progressing after failure of previous taxane- and anthracycline-based therapy. An expanded access program was initiated to provide access to capecitabine for patients who were not eligible for other capecitabine investigative protocols.

Methods: All patients had progressive disease after having received at least two chemotherapy regimens, one of which contained paclitaxel or docetaxel for metastatic disease. Data are currently available on 631 patients who received outpatient treatment with the standard dose of oral capecitabine (1250 mg/m^2 twice daily on days 1-14 of a 21-day treatment cycle) up to a maximum of 16 cycles.

Results: At study entry, the mean age of patients was 54.1 ± 10.3 years, 79% had a KPS of 7090, and the majority (94%) had metastatic disease. The mean duration of capecitabine treatment was 3.9 ± 3.6 (range 0-24.8) months, given at a mean daily total dose of 4116 ± 593 mg. In the 349 patients evaluable for efficacy, an objective response rate of 35% (CR 3%, PR 32%) and disease stabilization in 47% of patients was recorded. The estimated median time to treatment failure and median overall survival were 3.0 months (n=592; 95% CI, 2.8-3.5 months) and 10.2 months (n=569; 95% CI, 8.6-15.6 months), respectively. Overall, 528/631 (84%) patients experienced at least one adverse event, the majority of which were mild to moderate and affected the gastrointestinal tract (58%) or skin and subcutaneous tissue (44%). The most common treatment-related grade 3/4 adverse events were diarrhea (9%), vomiting (3%) and hand-foot syndrome (8%). Grade 3/4 myelosuppression was rare (neutropenia, 1%; thrombocytopenia, 2%) and no grade 3 alopecia was reported (grade 2, 0.3%). Dose modification due to adverse events was reported for 180 (29%) patients.

Conclusions: The results achieved in this heavily pretreated population confirm previous findings that capecitabine monotherapy is active, well tolerated and provides convenient outpatient therapy for patients with advanced and/or metastatic breast cancer refractory to previous treatment, including taxanes.

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Improving clinical outcomes and treatment convenience with oral ibandronate for metastatic bone disease

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Background: Standard therapy for metastatic bone disease (MBD) currently involves intravenous (i.v.) infusion of bisphosphonates, which target the underlying pathological processes of osteclast-mediated bone resorption to reduce skeletal complications. However, the requirement to visit hospital regularly for i.v. administration of a supportive care agent is inconvenient for patients, and may impact upon their quality of life. The clinical usefulness of i.v. bisphosphonates may occasionally be limited by a deterioration in renal function which, if patients are not closely monitored, can rarely progress to renal failure. Additionally, parenteral administration costs and staff time requirements add to treatment costs. Although oral bisphosphonate therapy is available, its use in practice is limited by concerns with regard to efficacy and the potential for gastrointestinal adverse effects. To improve clinical outcomes and treatment convenience for patients with MBD, there is a clinical need for an oral bisphosphonate that would allow ambulatory at-home administration, without compromise of efficacy or safety. The efficacy and safety of the oral formulation of ibandronate, a highly-potent, third-generation bisphosphonate, has been evaluated in phase III clinical trials of patients with metastatic breast cancer.

Patients and methods: In two randomized, multicenter studies, patients with MBD from breast cancer were randomized to treatment with oral ibandronate 50mg (n=287) or placebo (n=277). A multivariate Poisson regression analysis of pooled data from these studies assessed the number of skeletal related events arising in each treatment group during the 96-week treatment period. Metastatic bone pain was assessed on 7-point scale (from 0=none to 6=requiring >100mg/day morphine or equivalent), and patient quality of life was assessed using the EORTC QLQ-C30 questionnaire. Treatment-related adverse events were continually monitored.

Results: Oral ibandronate 50mg provided a significant (38%) reduction in the risk of new skeletal events compared with placebo (p=0.0001). Bone pain scores were significantly reduced from baseline (p=0.001) and maintained below baseline for the two-year study duration. Quality of life deterioration over time (commonly seen with MBD) was significantly reduced with oral ibandronate (p=0.03 vs placebo). Oral ibandronate was well-tolerated, with few gastrointestinal side effects and renal toxicity similar to placebo.

Conclusions: Oral ibandronate 50mg significantly improves clinical outcomes in patients with MBD, with efficacy comparable to zoledronate. As was demonstrated in a trial of i.v. ibandronate 6mg i.v. [1], statistically significant reductions in the risk of skeletal complications and bone pain with oral ibandronate were accompanied by quality of life benefits. Patients receiving oral ibandronate do not require hospital visits solely for administration of bisphosphonate therapy, resulting in improved treatment convenience for patients who have completed chemotherapy. Oral ibandronate would also permit convenient at-home administration in conjunction with other oral therapies (including hormonal therapy) and would ameliorate the bone mineral loss associated with some of these treatment strategies. The efficacy of oral ibandronate in reducing symptoms and complications of MBD, coupled with low gastrointestinal and no significant renal toxicity risk, provides effective therapy with reduced management costs, particularly for patients who are likely to receive bisphosphonate therapy for more than 6 months.

Reference

[1] Body et al. Ann Oncol in press.