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Mitomycin-C, 5-FU, Folinic Acid (Mi–Fu–Fo) as salvage chemotherapy for hepatic failure due to liver metastases in breast cancer

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Background: Patients with an impaired liver function as a result of liver metastases in breast cancer have a decreased possibility of treatment. Most cytotoxic agents are excreted via the bile and are therefore contraindicated in cases of impaired liver function.

Patients and Methods: In a phase II trial, patients with measurable liver metastases due to breast cancer and elevated liver enzymes were treated with Mitomycin C 8 mg/m^2 on day 1, 5-Fluorouracil (5-FU) 750 mg/m^2 and Folinate 300 mg/m^2 on day 1 and 2 every four weeks. WBC and platelets of 1.0 and 100 g/l, respectively, were required before each new cycle otherwise the cycle was delayed for one week.

Results: 30 heavily pretreated patients (median number of previous chemotherapies: 3) with a median age of 51 (range, 33–74) were enrolled. All had liver metastasis and elevated liver function tests defined as follows: liver enzymes* 1.5×UNL + AP *2.5×UNL or liver enzymes *3×UNL; 18 patients had hyperbilirubinaemia. The median number of administered cycles was 4. The liver enzymes decreased below two times upper normal level (UNL) in all patients who received more than 1 cycle. Myelosuppression was the main toxicity. Neutropenia grade 4 led to fever in 2 patients, and one patient developed a panaritium with sepsis. The median time to progression was 4.5 months and 7.0 months in patients who responded to the therapy, but the duration of response was 6.25 months. The median overall survival for the whole population was 6 months and in the group of responding patients 12.0 months. 6 patients had a partial remission, 12 patients had stable disease, 6 patients progressed during treatment, and 7 patients died after the first cycle. None of the patients with ascites responded.

Conclusion: Mi–Fo–Fu could control the disease in 40% of the patients, is a tolerable regimen and therefore a therapeutical option for heavily pretreated patients with liver metastasis and impaired liver function.

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Oral ibandronate: an effective, well-tolerated and convenient alternative to intravenous bisphosphonates for patients with breast cancer and bone metastases

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Background: Intravenous bisphosphonates are the current standard of care for the prevention of bone events in patients with metastatic bone disease. However, regular infusions impose a time burden on nursing staff, and scheduling difficulties with patients receiving chemotherapy occur. Regular hospital visits may be inconvenient for patients not receiving intravenous chemotherapy, taking several hours for travel, infusion and serum creatinine monitoring. Currently, the use of oral bisphosphonate therapy is limited by low efficacy compared with intravenous bisphosphonates, inconvenient dosing and gastrointestinal adverse events (AEs). The efficacy and safety of oral ibandronate, a newly approved aminobisphosphonate for the prevention of skeletal complications, has been evaluated in phase III clinical trials of patients with metastatic breast cancer.

Methods: A pre-specified pooled analysis was conducted on data from two multicenter, double-blind studies, in which patients were randomized to ibandronate 50 mg (n=287) or placebo (n=277) once-daily. A multivariate Poisson regression analysis assessed the risk of skeletal-related events (SREs). Bone pain was measured on a 5-point scale (from 0=none to 4=intolerable), and quality of life (QoL) was evaluated using the EORTC QLQ-C30. Drug-related AEs were monitored.

Results: Oral ibandronate significantly reduced the risk of SREs compared with placebo (38% reduction, RR 0.62, p=0.0001). Mean baseline bone-pain score was significantly reduced in the oral ibandronate group (−0.10 versus +0.20 with placebo, p=0.001) and maintained below baseline for 2 years. Oral ibandronate significantly improved global QoL (p<0.05), physical functioning (p<0.05) and role functioning (p<0.01), and had a renal AE profile similar to placebo. There were very few serious drug-related gastrointestinal AEs (incidence comparable with placebo).

Conclusions: Once-daily administration of oral ibandronate 50 mg provides a well-tolerated and effective alternative to existing intravenous aminobisphosphonates. The efficacy results were comparable to phase III study results with intravenous ibandronate 6 mg [1]. Long-term use of oral ibandronate would optimize treatment convenience for patients, and eliminate the substantial healthcare costs associated with bisphosphonate infusions and patient monitoring.

References

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A phase I trial evaluating the safety and immunogenicity of a HER-2 protein vaccine in patients with breast cancer

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Background: HER-2 Protein AutoVacTM (PX 104.1.6, Pharmexa A/S, Denmark) is a therapeutic vaccine designed to target HER-2 over-expressing tumours. HER-2 Protein AutoVacTM encodes a modified HER-2 antigen including two highly immunogenic peptides derived from tetanus toxin. Pre-clinical testing in cynomolgus monkeys has demonstrated that the vaccine was well-tolerated and induced significant HER-2 specific antibody titres [1].

The objective of the current phase I trial was to evaluate the short-term safety and immunogenicity of intramuscular injections with HER-2 Protein AutoVacTM in breast cancer patients.

Material and methods: Women with breast cancer (stage II, III or IV with no evidence of disease) expressing any positive degree of HER-2 by IHC or FISH and for whom there were no clinical indication for Herceptin, treatment were enrolled to a single dose, open-label phase I trial. The patients were immunized with 500 mg HER-2 Protein AutoVacTM at weeks 0, 2, 6 and 10 and subsequently monitored during a 6 week follow-up period. Patients who had at least one vaccination were included in the safety population. Adverse events (AE) were graded according to the NCI common toxicity criteria. Serum was collected at baseline and every second week to determine HER-2 specific IgG Antibodies (ELISA).

Preliminary Results: The preliminary results presented here are based on safety data obtained following 10 weeks treatment of all patients. Ten women (age: 35–66 yrs) with HER-2 over-expressing tumours (IHC 1+: n=5, 2+/3+: n=5) each received 4 immunisations with HER-2 Protein AutoVacTM. No serious adverse events have been reported. A total of 22 AEs (toxicity grade 1: n=20; grade 2/3: n=2) was reported in 9 patients. Nine AEs were possible/probably related to trial drug of which the most frequently reported event was grade 1 local injection site reaction (n=3).

Conclusion: Active immune-therapy with 4 repeated injections of HER-2 Protein AutoVacTM is well tolerated and safe in patients with HER-2 over-expressing breast cancer. Additional data including HER-2 specific antibody results will be presented at the congress.

References

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Intravenous and oral ibandronate provide long-term relief from bone pain in metastatic breast cancer

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Background: Two-thirds of patients with metastatic bone disease suffer significant symptomatic bone pain. Effective pain management is essential to reduce disability and improve quality of life (QoL). Yet in many patients, analgesics and conventional anti-cancer interventions (radiotherapy, chemotherapy, hormone therapy) fail to relieve pain adequately. The effect on bone pain and QoL with ibandronate, a newly approved bisphosphonate for skeletal metastases, has been investigated in phase III trials of patients with metastatic breast cancer.

Methods: International, multicenter, randomized, double-blind, placebo-controlled trials were conducted over a 96-week treatment period. In one trial, intravenous ibandronate 6 mg (n=154) was compared with placebo (n=158) infused over 1–2 hours every 3–4 weeks. In two further trials (data pooled, as pre-specified in the analysis plan), oral ibandronate 50 mg (n=287) was compared with placebo (n=277) once daily. Bone pain was assessed on a 5-point scale, from 0=none to 4=intolerable. QoL was evaluated using the EORTC QLQ-C30 questionnaire.

Results: Treatment with intravenous ibandronate 6 mg or oral ibandronate 50 mg rapidly reduced bone-pain scores and maintained them below baseline levels until the 2-year study endpoint. These reductions were statistically significant compared with placebo (intravenous ibandronate 6 mg, −0.28 versus +0.21, p<0.001; oral ibandronate 50 mg, −0.10 versus +0.20, p=0.001). Analgesic use was also significantly lower with oral ibandronate 50 mg versus placebo (p=0.019). Alleviation of bone pain with intravenous and oral ibandronate was accompanied by significant improvements in global QoL (p=0.004 and p=0.03 versus placebo, respectively). Compared with placebo, intravenous ibandronate also significantly improved physical functioning (p=0.034), emotional functioning (p=0.025) and social functioning (p=0.008), while oral ibandronate 50 mg significantly improved physical functioning (p<0.05) and role functioning (p<0.01).

Conclusions: Treatment with intravenous ibandronate 6 mg or oral ibandronate 50 mg significantly relieved bone pain in patients with bone metastases from breast cancer over 2 years of treatment. Sustained relief of bone pain allowed improved quality of life and mobility. Such benefits have not previously been reported with other bisphosphonates for metastatic bone disease.

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Long-term safety of oral ibandronate in patients with skeletal metastases from breast cancer: 4-year follow-up data

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Background: Long-term tolerability is an important consideration in the selection of bisphosphonates for metastatic bone disease, due to the lengthy duration of exposure needed to prevent bone events and help alleviate bone pain. Ibandronate is a newly approved bisphosphonate for the prevention of skeletal events in patients with breast cancer and bone metastases. The pooled results of phase III clinical trials have shown that oral ibandronate 50 mg once daily for 2 years has a safety profile comparable to placebo in metastatic breast cancer [1]. This abstract reports the results of non-controlled, follow-up studies that were conducted to examine the 4-year safety of oral ibandronate.

Methods: On completion of the 2-year placebo-controlled study period, patients received oral ibandronate 50 mg once daily for a further 2 years (n=115). Adverse events (AEs) and laboratory parameters were recorded.

Results: As might be expected with advanced cancer, 18% of patients did not complete the follow-up period due to AEs, and the majority of patients (83%) experienced at least one AE. Malignancy progression was the most commonly reported AE (52%), leading to the withdrawal of 11% of patients. AEs leading to withdrawal are summarized in Table 1.

Table 1.

	% patients (N)
Any AE	18.3 (21)
Malignancy progression	11.3 (13)
Esophagitis	1.7 (2)
Cerebral infarction	1.7 (2)
Bone pain	0.8 (1)
Back pain	0.8 (1)
Asthenia	0.8 (1)
Ascites	0.8 (1)
Renal AEs	0.0 (0)

Hypocalcemia (n=3), dyspepsia (n=3) and esophagitis (n=2) were the only AEs considered possibly related to oral ibandronate treatment by the study investigators. None of these AEs were serious or led to withdrawal from treatment. Oral ibandronate was not associated with any renal AEs or laboratory/vital sign abnormalities.

Conclusions: Oral ibandronate 50 mg is well tolerated for up to 4 years of treatment, with very few drug-related AEs and no renal AEs reported. These results suggest that oral ibandronate is particularly suitable for long-term administration at home, without the need for close AE monitoring.

References

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Local relapse and systemic recurrence in breast cancer patients. Are they related?

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Introduction: The main problem that still remains unresolved is to define a group of patients for whom local recurrence is a marker or a cause of systemic disease.

Materials and Methods: In order to examine the above mentioned issue we analysed data of 3110 operable breast cancer cases coming from Breast Oncology's Unit registry of IASO Women's Hospital, in Athens. Median follow up period was 52 months (1–344 months). The recorded characteristics are patients age, the type of surgery, the tumor's size and grade, the lymph nodes status, the estrogen and progesterone status, the presence of a lymphatic infiltration and Extended Intraductal Component. To account a systemic recurrence as a consequence of the local recurrence this should have followed in a time period shorter than 12 months. During the follow period we have observed 30 such cases (group 1). On the other hand, 94 patients did not present a systemic recurrence within 12 months after the local relapse (group 2).

Results: The two groups do not differ statistically significant for any of the recorded risk factors. More specifically, mean age was 53.55 and 52.33 years old in the two groups respectively (p-value=0.615). Two (6.7%) and 17 (18.1%) have lymphatic infiltration (p-value=0.157), 11 (36.7%) and 25 (26.60%) patients have EIC (p-value=0.365) in the two groups respectively. The tumor's size in 9 (30%) and 41 (43.6%) cases was 1–20 mm, in 19 (63.3%) and 47 (50.0%) it was 21–50 mm and in 2 (6.7%) and 5 (5.3%) the tumor's size was greater than 50 mm in the two groups respectively (p-value= 0.548). As the lymph nodes status is concerned, no statistically significant difference was found between the two groups (p-value= 0.770). Three patients in group 1 (10%) and 5 (5.3%) in group 2 had a grade I tumor, 17 (56.7%) patients in group 1 and 54 (57.4%) in group 2 had a grade II tumor while 10 patients (33.3%) in group 1 and 32 patients (34.0%) in group 2 had a grade III tumor (p-value= 0.7101). As far as the hormone receptors status is concerned, no significant difference was found (p-values= 0.444, 0.602).

Conclusion: Comparing the two groups with respect to the known risk factors we did not find any significant differences between them. The issue of the relation between local and systemic recurrence remain unsolved and further research is required.

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Zometa® (zoledronic acid) in patients with skeletal metastases secondary to breast cancer – a study of home versus hospital administration

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In patients with breast carcinoma zoledronic acid 4-mg (Z, Zometa®) has been shown to be significantly more effective than pamidronate 90-mg, reducing the risk of skeletal-related events by an additional 30% in patients receiving hormonal therapy (P=0.009) (Rosen et al. Cancer: 2003, 98(8)). It has the further advantage of being administered over only 15 minutes (every 3–4 weeks), allowing the possibility for home administration.

Aim: to compare quality of life (QoL) and pain scores in breast cancer patients receiving Z when administered either at home or in hospital, and to assess the safety of Z by performing serial evaluations of serum creatinine.

Design: breast cancer patients with at least one bone metastasis and receiving hormone therapy were recruited to the study. After a lead-in phase of 3 infusions of Z 4-mg in hospital (to ensure disease stabilisation on hormone therapy), 100 patients were randomised to receive 3 open-label infusions at home or in hospital, to be followed by a further 3 infusions at the opposite venue.

Method: the EORTC QoL scale (QLQ-C30) and brief pain inventory (BPI) were used to assess the potential benefits of Z treatment.

Results: 84 patients completed the study, with 79 available for analysis. Overall global health status, as measured by the QLQ-C30, showed a significant median improvement of 8.3% over the 9 infusions (P=0.0127). According to the BPI, there were significant reductions over the 9 infusions