271 POSTER

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.

272 POSTER

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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273 POSTER

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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274 POSTER

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.