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Infusion therapy of pamidronate in combination with radiation therapy in cancer patients with advanced, painful, metastatic bone lesions

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Introduction: Palliative radiation therapy is successful in the treatment of painful bone metastases; however, complete pain relief can be achieved only in about half of the patients and almost every fourth patient is refractory to such therapy. Pamidronate (Aredia®), a bisphosphonate, has shown substantial analgesia in patients with preceding radiation therapy and therefore is a promising candidate for a combination with radiation therapy.

Methods: In a prospective, randomized, double-blind, placebo-controlled, multicenter parallel group design, cancer patients with solitary or multiple painful, metastatic osteolytic bone lesions in the region of femur, humerus, pelvis or spine were treated with palliative radiation therapy (2 Gy/day for 18 to 23 days depending on type of tumor) and one of the following: placebo, 90 mg pamidronate on day 1, 15 and 29 (2-weekly) or on day 1 and 29 (4-weekly interval). Patients were followed up until month 12 after start of therapy. Response to treatment was defined by an at least 50% decrease of intensity of bone pain over at least four weeks as measured on item 3 (worst pain during the past 24 hours) of the Brief Pain Inventory.

Results: N = 76 patients were treated (55% females, median age: 66 years) in nine radio-oncological centers in Germany. Half of the patients (48.0%) in the placebo group responded to radiation therapy alone; under combined pamidronate therapy, responder rate was higher after 2-weekly (73.1%) than after 4-weekly (56.0%) application. Sample size was too low to confirm a superior efficacy of the 2-weekly pamidronate therapy over placebo (p = 0.10, one-sided exact Fisher test). Pain relief by 50% of the baseline value was achieved after 28, 32 and 34 days under pamidronate therapy in 2-weekly and 4-weekly intervals or under placebo. In contrast to the placebo group, no clear advantage of the 2-weekly compared to the 4-weekly interval could be detected in further outcome measures (pain scores, Karnofsky-Index, quality of life, analgesics consumption).

Conclusions: The results of this study appear to support the claim that radiation therapy combined with pamidronate 90 mg infusion therapy is superior to radiation therapy alone in reducing the pain in progressive painful metastatic bone lesions. There is no advantage of the 2-week application schedule if the two modes of application are compared. There were no new findings regarding the toxicity of the test drug such as vomiting or anemia.

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Transcriptome analysis reveals an osteomimetic phenotype for human bone metastatic breast cancer cells

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Breast cancer metastatic cells exhibit the selective ability to seed and grow in the skeleton. In this study, gene microarraying was performed on a model of breast cancer bone metastasis consisting of the MDA-MB-231 cell line and its variant B02, which is characterized by a high affinity for bone in vivo. Analysis of B02 cells transcriptional profile revealed that 11 and 9 out of the 50 most up- and down-regulated genes, respectively, overlapped with genes expressed by cells of the osteoblastic lineage. For example, B02 cells surexpress osteoblast specific cadherin-11, which mediates the differentiation of mesenchymal cells into osteoblastic cells. In contrast, S100A4, recently described as a key negative regulator osteoblast differentiation, was the most down-regulated gene in B02 cells. We established a list of differentially expressed genes compatible with the acquisition of an osteomimetic phenotype by B02 breast cancer cells. RT-PCR and western blotting experiments allowed us to validate the modulation of several candidate genes. Finally, we verified the pathophysiological relevance of our data using immunohistochemistry on human breast primary tumors and matched liver and bone metastases. This is the first large-scale depiction of the osteomimetic phenotype adopted by bone metastatic breast cancer cells. Our results provide with well-built basis for functional studies aimed at the understanding of the molecular mechanisms that govern bone metastasis development.

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Extended survival in women receiving trastuzumab for brain metastases from HER2 positive metastatic breast cancer

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Aim: To assess survival of patients with brain metastases (BM) from HER2 positive metastatic breast cancer (MBC) treated with trastuzumab after diagnosis of BM.

Historical series indicate that symptomatic BM develop in 10–16% of patients with MBC, and are associated with a median survival of 3–6 months. The increased incidence of BM (28–43%) in patients receiving trastuzumab for HER2 positive disease is well recognised, but increasingly apparent is the favourable prognosis of such patients if trastuzumab is continued.

We have performed a retrospective review of 71 assessable patients treated at our institution who have received anti-neoplastic treatment for BM between May 2002 and April 2005. HER2 positivity was defined as 3+ on immunohistochemistry or positive on fluorescence in-situ hybridization (FISH).

The median survival after diagnosis of BM in patients in whom HER2 status was negative or unknown (n = 49) measured 3 months, with 8.1% (95% CI 3.2%-19.2%) of patients alive at 1 year; patients with HER2 positive disease who did not receive trastuzumab after diagnosis of BM (n = 8) had similar median (3 months) and 1 year (12.5%) survival. In contrast, the median survival of women with HER2 positive disease treated with trastuzumab after diagnosis of BM (n = 14) was significantly longer at 12 months (p = 0.002), with 57.1% (95% CI 32.6%-78.6%) alive at 1 year. Notable within this group are several patients with multiple BM who have displayed responses or prolonged stabilization of central nervous system (CNS) disease to systemic anti-neoplastic therapies added to trastuzumab.

Our experience confirms the favourable prognosis of patients with HER2 positive BM treated with trastuzumab after diagnosis of CNS metastases. While this improvement in survival may result from better control of systemic disease, another possibility is that trastuzumab may also have a beneficial effect on BM. Although trastuzumab does not cross the blood brain barrier (BBB) under physiological conditions and fails to accumulate in cerebrospinal fluid after intravenous administration, the disturbed BBB evident in BM may allow accumulation of sufficient concentrations within metastases to synergise with chemotherapy and radiotherapy, phenomena well demonstrated in preclinical work. Prospective confirmatory studies are required.

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A Phase II trial of letrozole in combination with bevacizumab in patients with hormone receptor-positive metastatic breast cancer: Correlation of response with circulating endothelial (CEC) and epithelial cells (CTC)

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Background: Bevacizumab (B) added to chemotherapy prolongs PFS and OS in patients (pts) with metastatic breast cancer (MBC). In animal models of breast cancer, estrogen induces expression of VEGF that is suppressed by aromatase inhibition, suggesting that the combination of an aromatase inhibitor and B may be more effective than either agent alone. We performed a feasability study testing B with letrozole (L) for the treatment of hormone-receptor positive MBC. Identifying clinically relevant intermediate markers for angiogenesis that might predict response has been difficult, although CECs have been proposed as a marker of tumor progression and/or response to antiangiogenic therapy with B. We have previously shown that change in CEC predicts stable disease at first evaluation in a phase II study of erlotinib and B (Rugo, ASCO 2005). To explore markers of activity and response to B and L, we assayed CECs and CTCs at weeks 0 (baseline), 3, 12, and then Q 12 wks.

Methods: Eligible pts have MBC, are postmenopausal and are candidates for AI therapy. Prior non-steroidal AI use without progression is permitted. Therapy consists of L (2.5 mg daily) and B (15 mg/kg IV q3 weeks). A total of 42 pts will be enrolled in a two-step design; the primary endpoint is toxicity. CECs are defined as CD34/31+, CD45-. Progenitor