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The Safety of Chemotherapy for Breast Cancer Patients With Hepatitis C Virus Infection

Y. Miura[1], Y. Naito[1], A. Shimomura[2], T. Iwatani[2], D. Miura[2], H. Kawabata[2], T. Takano[1]. [1]*Toranomon Hospital, Department of Medical Oncology, Tokyo, Japan;* [2]*Toranomon Hospital, Department of Breast and Endocrine Surgery, Tokyo, Japan*

Background: Hepatitis C virus (HCV) infection is one of the major causes of chronic liver disease, and more than 1.5 million people are infected with HCV in Japan. However, little information on the status of HCV during chemotherapy for solid tumours is available, and the influence of HCV infection on toxicity of chemotherapy is unknown.
Material and Methods: We performed a retrospective survey of 1,110 patients diagnosed with breast cancer between January 2006 and March 2011 at our institution. This survey included 23 patients who were positive for anti-HCV antibodies. We retrospectively investigated the change in HCV load and the toxicities of chemotherapy for HCV-infected patients with breast cancer, using their medical records.
Results: Ten out of 23 HCV infected patients with breast cancer received chemotherapy. Their median age was 66 years (range: 50−77 years). Three patients had liver cirrhosis (one of them with Child B cirrhosis) at baseline. The remaining seven patients were diagnosed with chronic hepatitis, and their liver function tests and complete blood cell counts at baseline were normal. Chemotherapy included epirubicin and cyclophosphamide (EC) (n = 3), EC followed by docetaxel (n = 1), EC followed by paclitaxel (n = 1), docetaxel, cyclophosphamide and trastuzumab (n = 2), trastuzumab alone (n = 2) and gemcitabine alone (n = 1). Four out of five patients who received anthracycline-based therapy developed grade 3−4 hematologic toxicities (grade 4 neutropenia [n = 4], grade 3−4 thrombocytopenia [n = 2]), and one patient developed febrile neutropenia. Serum HCV-RNA level before and after chemotherapy could be evaluated in six patients. Median serum HCV-RNA level at baseline and after chemotherapy was 6.5 and 6.7 logIU/ml, respectively. No patients demonstrated elevated transaminases and bilirubin level during and after chemotherapy.
Conclusion: Chemotherapy for breast cancer patients with HCV infection did not influence HCV load or liver function. However, hematologic toxicities might be exacerbated by HCV infection, especially in patients who received anthracycline-based chemotherapy.

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Renal Safety of Zoledronic Acid (ZOL) in Patients (pts) Starting ZOL Therapy and Beyond 2 Years of Treatment − a Prospective Multi-center Evaluation

T. Van den Wyngaert[1], M. Delforge[2], C. Doyen[3], L. Duck[4], I. Delabaye[5], H. Wildiers[6], on behalf of BSMO/BHS and EPOZ/LOTUZ investigators. [1]*Antwerp University Hospital, Nuclear Medicine, Edegem, Belgium;* [2]*University Hospitals Leuven, Hematology, Leuven, Belgium;* [3]*Cliniques Universitaires UCL, Hematology, Godinne, Belgium;* [4]*Clinique St.-Pierre, Medical Oncology, Ottignies, Belgium;* [5]*Novartis Pharmaceuticals, Novartis Oncology, Vilvoorde, Belgium;* [6]*University Hospitals Leuven, Medical Oncology, Leuven, Belgium*

Background: Data on the renal safety of zoledronic acid beyond two years of therapy are scarce.
Materials and Methods: Renal deterioration (RD) was prospectively assessed in two phase 4 multi-center studies enrolling pts starting ZOL treatment (group A) or with ⩾ 2 years of ZOL therapy (group B). All pts in group A received 4 mg (or dose adjusted to renal function) of ZOL given IV q3−4w, but dose and regimen were per physician's discretion in group B. Except for other bisphosphonates, any concomitant anti-cancer therapy was allowed. RD was defined using established criteria: doubling in serum creatinine, or increase of 0.5 or 1.0 mg/dL, if baseline creat was lower or higher than 1.4 mg/dL, respectively. RD was deemed irreversible if values did not return to within 10% of baseline during follow-up. At 6 months, incidence rates (IR) of a first episode of RD were calculated. Cox regression was used for group comparisons.
Results: In 587 pts (group A=308; group B=278) 2,641 ZOL administrations and creat samples were studied during 238 patient years follow-up. Median age of these 215 men and 372 women was 67 years (range 22−90) and pts had breast- (47%), prostate cancer (13%), multiple myeloma (MM) (20%), or another malignancy (20%). Group B had more MM pts (30% *vs* 10%), while other histologies were more frequent in group A (35% *vs* 4%), likely due to differences in survival. Median duration of ZOL use in group B at baseline was 38 months (range 24−80). The median number of ZOL infusions in both groups was similar (group A=6; group B=5; Mann-Whitney $p = 0.77$).
Overall, the IR per person-year of RD using creatinine thresholds was 3.8% (95% CI 2.0−7.4%), with a total of 9 episodes. Only 1 event was reversible (11%). The annual RD rate was numerically lower in group B (HR 0.34; 95% CI 0.08–1.35; $p = 0.13$), with an IR of 2.3% (95% CI 0.7−7.1%; 3 events) compared to 5.7% (95% CI 2.5–12.8%; 6 events) in group A. In a sensitivity analysis, pts >75 years had a higher RD rate (HR 5.84; 95% CI 1.57–21.7; $p = 0.009$), but primary malignancy was not a predictor of RD. The analysis did not correct for use of other nephrotoxic drugs.
Conclusions: In pts receiving anti-cancer therapy and ZOL, the annual rate of a first episode of RD was 3.8% using established creatinine thresholds. This rate is lower (albeit not statistically significant) in patients with ⩾2 y of ZOL therapy compared to patients starting ZOL treatment, indicating no clinically relevant renal safety issues with long term ZOL use.

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Prevention of Skeletal-Related Events With Denosumab or Zoledronic Acid − Combined Analysis From 3 Registrational Trials

A. Lipton[1], K. Fizazi[2], A.T. Stopeck[3], D.H. Henry[4], J.E. Brown[5], F. Saad[6], D. Yardley[7], P. Maroto[8], C. Ke[9], S. Jun[9]. [1]*Pennsylvania State University, Milton S Hershey Medical Center, Hershey, USA;* [2]*University of Paris Sud, Institut Gustave Roussy, Villejuif, France;* [3]*University of Arizona, Arizona Cancer Center, Tucson, USA;* [4]*Joan Karnell Cancer Center, Philadelphia, USA;* [5]*Cancer Research UK Clinical Centre, Leeds, United Kingdom;* [6]*University of Montreal Hospital Center, Montreal, Canada;* [7]*Sarah Cannon Research Institute and Tennessee Oncology PLLC, Nashville, USA;* [8]*Hospital de La Santa Creu i Sant Pau, Barcelona, Spain;* [9]*Amgen Inc., Thousand Oaks, USA*

Background: Patients (pts) with metastatic bone disease are at increased risk for skeletal-related events (SREs). A planned analysis of data from 3 large phase 3 trials showed denosumab was superior to zoledronic acid (ZA) in delaying time to 1st on-study SRE (HR = 0.83 [95% CI: 0.76, 0.90]; P < 0.0001) among pts with a broad range of tumour types and bone metastases (mets). We now compare treatment with denosumab vs ZA on time to 1st SRE by age group and SRE type, time to 1st SRE or hypercalcemia of malignancy (HCM), skeletal morbidity rate (SMR), and change in bone markers in this population.
Methods: Adult pts with solid tumours or multiple myeloma and bone mets were randomized to 120 mg SC denosumab or 4 mg IV ZA (adjusted for renal function) every 4 weeks. Daily calcium (⩾500 mg) and vitamin D (⩾400 IU) supplements were advised. For this planned analysis, patient-level data was combined from 3 identically designed, double-blind, double-dummy phase 3 trials (Clinicaltrials.gov id: NCT00321464, NCT00330759, NCT00321620; sponsor Amgen). Time to 1st SRE was analyzed by a Cox proportional hazards model. The Wei, Lin, and Weissfeld model was used to test for heterogeneity of the effect of denosumab across the 4 types of SREs (pathological fracture, radiation or surgery to bone, or spinal cord compression). These trials are completed.
Results: A total of 5723 pts enrolled (2862 denosumab; 2861 ZA). Cancer types included breast (36%), prostate (33%), other solid tumours (28%), and myeloma (3%). While on study, 32.6% of denosumab and 37.8% of ZA pts experienced a SRE. The risk of 1st on-study SRE was significantly lower with denosumab vs ZA in pts <65 years old (HR 0.82 [95% CI: 0.73, 0.93], P = 0.002) and ⩾65 years old (HR 0.82 [95% CI: 0.72, 0.94], P = 0.004). The effect of denosumab was consistent across SRE type. Radiation to bone and pathological fracture occurred more often than spinal cord compression or surgery to bone. Compared with ZA, denosumab significantly delayed time to 1st radiation to bone and pathologic fracture (Table), significantly prolonged time to 1st SRE or HCM (HR 0.83 [0.76, 0.90]; p < 0.0001), and significantly reduced SMR (0.69 vs 0.81 events/yr; P < 0.0001). Median reduction from baseline in urinary N-telopeptide corrected for serum creatinine was significantly greater with denosumab than ZA (80% vs 68%; P < 0.001). Most patients (97%) reported adverse events; the most common were nausea (31%), anemia (29%), and fatigue (27%).

Table: Time to 1st SRE by SRE type

	n	Hazard ratio (95% CI)	P-value
Radiation to bone	1134	0.77 (0.69, 0.87)	<0.0001
Pathologic fracture	1133	0.86 (0.76, 0.96)	0.0093
Spinal cord compression	162	0.89 (0.65, 1.21)	0.46
Surgery to bone	135	0.86 (0.61, 1.21)	0.38

Conclusion: In these patients, treatment with denosumab vs ZA delayed the time to all SRE types, significantly decreasing the 2 most common SRE types, prolonged the time to 1st SRE or HCM, and reduced SMR and bone markers.