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Incidence of bisphosphonate associated osteonecrosis of the jaws

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Background: Bisphosphonates are used in the treatment of patients with metabolic bone diseases and in malignant diseases with metastasis to the bone. One side effect is Bisphosphonate associated osteonecrosis of the jaws (BP-ONJ) which has been known for 6 years now. The exact incidence of BP-ONJ is discussed in controversy.
Material and Methods: In a PubMed literature review using the search terms: "bisphosphonate", "diphosphonate", "osteonecrosis", "incidence" and "prevalence", articles were identified and scanned for incidence rates. Further articles from the references were included. The published incidences were correlated to the study design.
The study designs were grouped to retrospective studies, in cross sectional or prospective studies. A further criterion was the presence of oral and maxillofacial examinations conducted by a dentist, oral surgeon or oral- and maxillofacial surgeon.
Results: 27 articles (15 retrospective, 3 cross sectional, 6 prospective studies, 1 web survey, 1 estimation and 1 study with an unclear design) reported incidences or prevalences of BP-ONJ. 17 articles reported on multiple myeloma patients, 11 articles on breast cancer patients and 5 reported on prostate cancer patients.
The average incidences for all breast cancer patients were 4.6% (1−11%), for multiple myeloma 7.6% (3−21%) and for prostate cancer 10.3% (3.0−19%). Including only cross sectional or prospective studies, the incidences change to 4.5% (3−11%) for breast cancer, 14.1% (7−21%) for multiple myeloma and 19% (19%) for prostate cancer. Including studies with a cross sectional or prospective design and an oral examination, the incidences increase to 8.5% (6−11%) for breast cancer, 19% (17−21%) for multiple myeloma and 19% (19%) for prostate cancer.
Conclusions: The incidence of BP-ONJ correlates with the study design. Breast cancer patients might have a lower risk of developing BP-ONJ. Recently conducted prospective or cross sectional studies with oral examination reveal higher incidences compared to studies with no oral examination or studies with a retrospective design. Reasons for this might be that in older studies the more potent bisphosphonates that are more often associated with BP-ONJ were not in use, and due to the oral examination BP-ONJ was detected at earlier asymptomatic stages. Therefore the incidence of BP-ONJ might be underestimated to date.

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Independent central review of clinical benefit rates in FIRST: a Phase II comparison of fulvestrant 500 mg with anastrozole 1 mg as first-line endocrine therapy for postmenopausal women with hormone receptor positive advanced breast cancer

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Background: A Phase II open-label, randomised, multicentre study was conducted to compare fulvestrant (Faslodex™) 500 mg (HD) versus anastrozole (Arimidex™) 1 mg as first-line treatment for postmenopausal women with advanced breast cancer. The primary endpoint was clinical benefit rate (CBR, ie the proportion of patients achieving a complete response, a partial response or stable disease for $\geqslant$24 weeks). A prospectively-planned independent central review of radiological data was conducted.
Materials: Scheduled tumour assessments were performed every 12 weeks, using RECIST criteria, until objective progression or an event necessitating discontinuation. As a modification to RECIST, patients with bone metastasis (lytic or mixed) as a single site of disease were eligible for the study. All patients with metastatic bone lesions at baseline (confirmed by plain X-ray, CT or MRI scan) have isotopic bone scans or skeletal surveys every 24 weeks until progression. All available radiological data were collected by an independent review (IR) facility. Single read was performed in a blinded fashion for each subject. A summary of best overall response for each reviewed patient was compared with the investigator-determined results by means of a discrepancy table assessing the proportion of patients in each arm with and without clinical benefit (CB).
Results: In total, 205 women (median age 67 years) were included (fulvestrant HD: n = 102; anastrozole: n = 103). CBR was similar between treatments: fulvestrant HD 72.5%, anastrozole 67.0% (odds ratio 1.3023, 95% confidence interval 0.7170, 2.3976, p = 0.3860). Images were available for IR from 93% of 205 randomised patients, 95 from each study arm. CBRs of 75% and 72% (investigator) and 69% and 66% (IR) were assigned to patients in the fulvestrant- and anastrozole-treated arms, respectively. This gave concordance rates of 88.4% and 86.3% for fulvestrant and anastrozole, respectively. 18 patients assigned to 'no CB' by IR were considered to have CB by the investigator (8/29 on fulvestrant, 9/32 on anastrozole). A smaller number of patients (7/51) were assigned to CB by IR and not by the investigator (3/24 on fulvestrant, 4/27 on anastrozole).
Conclusion: There was no evidence of bias in the assessment of the primary endpoint of CBR in this study. The potential for site bias in open-label multicentre trials in an advanced breast cancer setting supports the use of central review of imaging data.

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Lapatax: Safety profile of neoadjuvant lapatinib combined with docetaxel in Her 2/neu overexpressing breast cancer – EORTC protocol 10054

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Objective: To assess the safety/tolerability of the combination lapatinib (L) and docetaxel (D) in patients with Her 2/neu overexpressing breast cancer (BC). This study is important as it will define how to deliver lapatinib with taxotere, a highly active drug in breast cancer.
Patients and Methods: Female patients (pts) with locally advanced, inflammatory or large operable BC were treated with escalating doses of L from 1000 to 1250 mg/day, in combination with D given IV every 21 days at doses ranging from 75 to 100 mg/m^2 for 4 cycles. At least 3 pts were treated at each dose level. The definition of dose limiting toxicity (DLT) is based on the toxicity assessed at cycle 1 as follows: any grade 3−4 non hematological toxicity, ANC < 0.5 G/L lasting for 7 days or more, febrile neutropenia or thrombocytopenia <25 G/L. GCSF was not permitted as primary prophylaxis. Core biopsies were mandatory at baseline and after cycle 4. Pharmcokinetic (PK) samples were collected on day 1 of cycles 1 and 2.
Results: To date, 18 pts with a median age of 53 years (range 36−65) have been enrolled at 5 Dose Levels (DLs). The toxicity profile for 18 patients (68 documented cycles) is summarized below. At DL5 (1000/100), 2 pts had DLTs (neutropenia grade 4 $\geqslant$7 days and febrile neutropenia), and 3 additional pts were enrolled with primary prophylactic G-CSF. As expected, the safety profile improved and the dose escalation will continue with prophylactic G-CSF to investigate DL6 (1250/100). These findings are consistent with published Phase I data for this combination [1].

N = 18 patients n (%)	Grade 1	Grade 2	Grade 3	Grade 4
neutropenia	1 (6)		3 (17)	13 (72)
febrile neutropenia			2 (11)	
fatigue	8 (44)	7 (39)		
diarrhoea	9 (50)	3 (17)		
pain: joint/muscle/other	5 (28)/4 (22)/3 (17)	4 (22)/4 (22)/3 (17)	0/0/1 (6)	
constipation	2 (11)	3 (17)	1 (6)	
elevated transaminases SGPT/SGOT	7 (39)/5 (28)			

Conclusions: The main toxicity of the L + D combination is haematological and was reached at DL5 (1000/100), without primary GCSF. An additional DL6 with primary prophylactic GCSF is being investigated (1250/100). PK data will be presented at the meeting plus the recommended dose for phase II studies.

References

[1] LoRusso PM, Jones SF, Koch KM, et al. Phase I and pharmacokinetic study of lapatinib and docetaxel in patients with advanced cancer. J Clin Oncol 2008, 26(18):3051–3056.