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Zoledronic acid (Zometa), a new potent bisphosphonate, reverses mechanical allodynia and limb sparing in a rat model of bone cancer pain

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Purpose: Severe pain is one of the most common complications of metastatic bone disease. Zoledronic acid (ZOL) is a novel bisphosphonate with an imidazole substituent, currently in phase 3 clinical development for the treatment of both malignant bone disease and osteoporosis. ZOL has previously been shown to potently inhibit osteoclastic bone resorption, lytic bone metastases and angiogenesis in preclinical models. This present study investigated the effect of ZOL on pain in a new rat model of bone cancer pain.

Methods: Adult female rats were given intra-tibial injections of MRMT-1 rat mammary gland carcinoma cells (3 ul, 10 million cells/ml). These animals gradually develop mechanical hyperalgesia, mechanical allodynia (skin hypersensitivity to non-noxious stimuli) and hind limb sparing, beginning on day 12-14 following cell injection. ZOL was administered 3 times a week (10 and 30 ug/kg s.c.) from the day of cell injection, allodynia and limb sparing were then repeatedly measured for up to 21 days.

Results: ZOL produced a profound inhibition of hind limb sparing and mechanical allodynia. In comparison to vehicle-treated controls, which showed maximal hind limb sparing by day 19, rats given the higher ZOL dose did not develop any sign of hind limb sparing over 19 days following intra-tibial cell injection. However, when administered as a single injection (100 ug/kg, s.c.) on day 19, ZOL had no acute effect. By contrast, acute treatment with morphine (1-10 mg/kg, s.c.) produced a dose-dependent reduction in mechanical allodynia and, at the highest dose only, also a significant reduction in hind limb sparing.

Conclusion: Alleviation of bone pain is a frequent clinical observation in cancer patients treated with bisphosphonates but the mechanism of action remains unclear. This new rat model should facilitate further studies on the pathophysiology of bone cancer pain and its amelioration by bisphosphonates. The marked beneficial effects observed with ZOL in the rat model indicate that the compound has the potential to reduce pain in cancer patients with bone metastases.

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Functional spectrum of an HPTLC analysis station in a hospital pharmacy quality assurance program

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Purpose: As a part of the development of a quality-assurance program (QAP), an analytical platform was installed in the Department of Clinical Pharmacy. This platform consists in two analytical units: the first one uses high-performance thin-layer chromatography (HPLTC) combined with densitometry while the second one uses high-performance liquid chromatography (HPLC) combined with the most common detection modes and a powerful liquid chromatography-tandem mass spectrometry (LC/MS/MS) for structural analysis.

Methods: The HPTLC-CAMAG® consists in: an HPTLC-vario® development chamber, 2) TCL Sampler III® automated applicators, 3) teflon migration chambers and 4) a TLC Scanner 3® densitometer controlled by CATS 4® software. HPTLC allows to obtain chromatograms in 10 min, and run over a migration pathway of 5-6 cm. The plates are read by absorption-reflection or fluorescence-reflection at an ad hoc wavelength (190-800 nm). The peaks areas scanned are measured by the trapezoid method. The calibration curves are generated by Michaelis-Menten non-linear regression, and validated by internal quality control. The analytical yield is high, i.e., up to 50 assays and 250 determinations per day. HPTLC analysis covers a wide functional range; 1) as a teaching tool for separative analysis and GLP, 2) it is an invaluable method for the optimisation of mobile phases and for the determination of absorption spectra and absorption maxima, with the aim to developing HPLC methods in complex matrices, 3) it provides major support for post-production quality control of prescribed hospital preparations of all types e.g. those connected with narcotic analgesia (morphine, fentanyl, sufentanyl...), and off course chemotherapy (MTX, 5-FU, Ara-C, dFdC, CDDP, LOHP, ADM, DRB, 4-EPI, IDA, VP16, IFM, CPM). Furthermore, it can also be used for dry dosage analysis, 4) it is an useful tool in pharmaceutical assessment e.g., in studies on the substances physico-chemical characteristics (identity, purity, concentration, stability and compatibility) particularly with regards to generic products and 5) it can contribute to monitoring the container-content interactions.

Conclusion: HPTLC quantitative and qualitative analysis has now reached a remarkably high level of development and performance. After 30 months in operation and 25, 000 assays, the HPTLC analysis unit has become one of the mainstays of the Gustave-Roussy QAP with a cost of no more than 1.5 US$ per routine assay.

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Phase I-II study: clinical and pharmacokinetic data of docetaxel (DTX), carboplatin (CBDCA) and concomitant radiotherapy (RT) in stage IV head and neck cancer

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Purpose: In vitro studies showed that DTX and CBDCA combination enhances the effects of radiation more effectively than either drug separately. We investigated the pharmacokinetics of these drugs administered at low doses as radiosensitizer concomitant with hyperfractionated RT. Toxic effects and clinical efficacy were also studied.

Methods: 30 patients with unresectable stage IV squamous-cell head and neck cancer received RT (70Gy over 7 weeks, 5 days weekly) concurrent with CBDCA AUC 0,40min·mg/ml (20' i.v. infusion) from day 1 to 5 of weeks 1, 3, 5, 7 and DTX 30mg/m2 (1h i.v. infusion) on days 10, 24, 38. Site of disease: oropharynx, 14 patients; hypopharinx, 8; oral cavity, 5; larynx, 3. Nodal stage: N1, 2; N2, 18; N3, 10. In 11 patients a pharmacokinetic evaluation was done. Several blood samples were collected during and after anticancer agents administration;. The CBDCA plasma concentration was measured as ultrafiltrable free platinum by FAAS. We used HPLC analysis for DTX determination.

Results: The Cmax plasma levels of CBDCA ranged from 3361-2044 ng/ml (at 20') whereas Cmin was reached 5 h after i.v. administration. On 10thday mean DTX Cmax was 735 ng/ml, AUC 0,05min·mg/ml, clearance 65,14 l/h. At the end of locoregional treatment we had 22 CRs (73%) and 8 PRs (27%). After surgical salvage, the number of CRs increased to 24 (80%). Mucosal toxicity (grade III-IV in 21 patients = 70%) was the main dose-limiting toxicity. Grade III dermatitis and leukopenia was observed in 13 (43%) and 11 (36%) patients respectively.

Conclusions: CBDCA+DTX and concomitant RT is feasible and effective treatment in locally advanced head and neck cancer; acute mucosal and cutaneous toxicity were frequently severe but manageable. Concurrent CBDCA, DTX and RT do not alter pharmacokinetic drug behaviour respect single-agent data. During the first course of chemotherapy, the experimental AUC values and those calculated by Calvert formula were similar. However, during following weeks a progressive increase of platinum levels was observed. It could be assumed that a bias in dose calculation occurred because a non linear relationship between creatinine clearance and CBDCA clearance. Further investigation is needed to establish more clearly the significance of variation in free and bound Pt repeated courses of CBDCA administration.

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Feasibility of combination of cisplatin (CDDP) and gemcitabine (GEM) in non-small cell lung cancer and other solid tumors: analysis of dose-intensity (DI) and compliance of four different schedules

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The combination of CDDP plus GEM is active and improves survival in advanced NSCLC, but the optimal doses and timing to deliver both drugs is not yet well defined. Therefore, we analyzed the DI, toxicity and activity of four different schedules of CDDP and GEM in three different consecutive studies performed in our institution. Untreated patients with stage IIIA-B/IV NSCLC, ECOG PS < 2, adequate bone marrow, liver and renal function were enrolled. Toxicity was evaluated according to the SWOG criteria and DI was calculated with the method described by Hryniuk, as mgs per sqm per week during the whole treatment (day 1 of the first cycle to the last cycle day). Treatment programs were as follows: A) CDDP 70 mgs/sqm d2 + GEM 1000 mgs/sqm d1,8,15 q4W; B) CDDP 70 mgs/sqm d2 +