Supportive care agents

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BNP7787 as a potential protector of cisplatin-induced side-effects: step-wise reduction of the hydration schedule

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Preclinical studies in tumor models demonstrated protection against cisplatin-induced nephrotoxicity by BNP7787 with no evidence of tumor protection. A fraction of BNP7787 is rapidly converted to mesna in the kidneys, which in turn results in inactivation of the toxic monohydrated species of cisplatin. In a Phase I trial, BNP7787 was safe and well tolerated when given at doses of 4.1 g/m^2 up to 41 g/m^2 immediately preceding cisplatin 75 mg/m^2 (Ann Oncol 2000 (suppl 4);11:84). BNP7787 was also studied in pts with advanced solid tumors at a dose of 18.4 g/m^2 over a 15-min 300-ml infusion preceding a fixed dose of cisplatin 75 mg/m^2 over a 1-h 180-ml infusion administered every 3 weeks concurrently with step-wise reduction of the hydration schedule (cohorts of 6 pts, Groups A-D). Pts were not previously treated with cisplatin and baseline creatinine clearance was >60 ml/min. In Group A pts received 1000 ml NaCl 0.9% + supplements over 90 min and 100 ml mannitol 20% over 10 min preceding BNP7787 and 500 ml NaCl 0.9% + supplements over 30 min after cisplatin as their hydration schedule. Group B received 500 ml NaCl 0.9% over 60 min pre and 500 ml NaCl 0.9% over 30 min after chemotherapy. Group C received NaCl 0.9% 500 ml over 30 min pre chemotherapy only and in Group D no hydration was planned. All patients received antiemetics preceding cisplatin. Only 1/6 patients in a Group was allowed to develop grade I nephrotoxicity or creatinine clearance <60 ml/min on the day of the next cycle in order to enter pts into the next Group. The reduction of the hydration schedule was well tolerated in Groups A and B (cycles: range 1-6, median 2.5). In Group C (cycles: range 2-8, median 4) there were 2/6 pts with nephrotoxicity Grade 1 at the start of cycle 3. In conclusion, BNP7787 preceding cisplatin is potentially useful to reduce the hydration schedule as mentioned for Group B, thereby enabling cisplatin treatment in the outpatient clinic.

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Phase I and pharmacokinetics trial of BNP7787 in patients receiving cisplatin and paclitaxel for advanced Non-Small Cell Lung Cancer (NSCLC)

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Purpose: BNP7787 is a novel chemoprotectant for taxane and/or platinum therapy. In this phase I clinical study, safety and pharmacokinetics of BNP7787 are assessed in order to find a clinically recommended dose of BNP7787 and to investigate the effect of BNP7787 upon paclitaxel and cisplatin combination therapy.
Method: To be eligible, patients must have stage IIIB or IV NSCLC, 20-74 in age, PS 0 or 1, and adequate organ functions. Patients were intravenously infused with BNP7787 at dose of 4.1 to 41.0g/m^2 one week prior to chemotherapy, followed by combination chemotherapy of paclitaxel (175mg/m^2) in a 3 hours infusion and cisplatin (75mg/m^2) every 3 weeks with BNP7787 immediately before administration of cisplatin. Dose escalation of BNP7787 was permitted, if none of grade 2-4 toxicity by NCI-CTC induced by BNP7787 occurred in 3 patients.
Results: The pharmacokinetic parameters of BNP7787 at 18.4g/m^2 or greater satisfied the specified levels. None of grade 2 or more adverse drug reactions (ADRs) induced by BNP7787 was noticed in this study except grade 2 rash. Injection site pain (9 patients) was the most frequent ADRs, and the frequency increased with dose increase of BNP7787. Neutopenia was the most frequent toxicity with chemotherapy. No severe neurotoxicity was observed. Increased creatinine level and tinnitus were observed in only one patient, respectively. Although nausea and anorexia occurred at high frequency, vomiting was marginally identified at higher doses of BNP7787. Of 21 patients receiving chemotherapy, 9 showed partial response, and the overall response rate was 42.9%.
Conclusion: The data shows a good safety profile of BNP7787. Based on pharmacokinetic parameters, and as a result of overall evaluation of safety and efficacy of BNP7787, 18.4g/m^2 has been chosen as a clinically recommended dose to be used for the succeeding study. It has also been suggested that BNP7787 does not interfere with antitumor efficacy of the chemotherapy.

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Phase I study of oral gallium maltolate in patients with refractory malignancies

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Gallium maltolate is a new oral investigational agent in clinical testing as an antineoplastic agent and for treatment of skeletal related complications of malignancy. Gallium, the active element in gallium maltolate, is a metal that inhibits ribonucleotide reductase. Intravenous formulations have been shown to be effective for hypercalcemia of malignancy and potentially for direct treatment of cancers. Phase I trials of up to 5 doses of gallium maltolate in healthy volunteers or Paget';s disease patients indicate that gallium maltolate is well tolerated, has 30-50% bioavailability, achieves blood concentrations >500 ng/mL, and has a half-life of >120 hours. The current ongoing trial is designed to evaluate the pharmacokinetics and safety of oral gallium maltolate in patients with refractory malignancies and to determine the optimal dose for efficacy evaluations. Patients are randomized to receive 50 mg, 150 mg, or 500 mg daily doses of gallium maltolate for 28 days followed by a 14-day rest period. Demographics for the 21 enrolled patients are: median age 68 yrs (range 47-87 yrs); 18 males; 13 prostate cancers, 4 multiple myelomas, 3 lymphomas and 1 bladder cancer. Consistent with >120 hr half-life of total serum gallium, Cmax and Cmin increased over the 28-day treatment with values (ng/mL) of 74.1 and 73.5 at 50 mg (n=1), 90.8 and 96.0 at 150 mg (n=2), and 520.4 and 443.8 at 500 mg (n=4). Adverse events (AE) were mostly Grade 1 or 2, and no AEs related to gallium maltolate were reported. Ten of 20 patients had modest hemoglobin decreases (4 pts Grade 2, 6 pts Grade 1), and 3 patients had Grade 3 increases in alkaline phosphatase, none of which required dosage reductions. Other labs including platelets, WBC, creatinine, LDH and AST were not significantly changed. Patients with advanced cancer tolerate gallium maltolate very well. Serum levels of total gallium are in the range expected to have clinical activity. Based upon these results, Phase II testing in myeloma, lymphoma, prostate cancer, and bladder cancer is planned to commence shortly.

Cyclins and CDKs

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Cytoplasmic re-localization and inhibition of the cyclin-dependent kinase inhibitor p27Kip1 by Akt-mediated phosphorylation in breast cancer

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The cyclin-dependent kinase inhibitor p27kip1 is a putative tumour suppressor for human cancers. The mechanism underlying p27kip1 deregulation in human cancer is poorly understood. We demonstrate that Akt, a serine/threonine kinase frequently activated in human cancer, regulates cell proliferation in breast cancer cells by preventing p27kip1–mediated growth arrest. Threonine 157 (T157), which maps in the nuclear localization signal of p27kip1, is a major Akt-phosphorylation site. Akt-induced T157 phosphorylation causes retention of p27kip1 in the cytoplasm, so precluding p27kip1-induced G1 arrest. Conversely, the p27kip1-T157A mutant accumulates in cell nuclei and Akt does not affect p27kip1-T157A-mediated cell cycle arrest. Lastly, T157-phosphorylated p27kip1 accumulates in the cytoplasm of primary human breast cancer cells parallel to Akt activation. Thus, cytoplasmic re-localization of p27kip1, secondary to Akt-mediated phosphorylation is a novel mechanism whereby the growth inhibitory properties ofp27kip1 are obstructed and the proliferation of breast cancer cells is sustained.