516

Novel 2-step desensitization dosing regimen of intravenous PV701, an oncolytic virus, results in improved tolerability: a phase I study of patients with advanced solid tumours

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Background: PV701 is an oncolytic Newcastle disease virus that is active preclinically when given intravenously (IV). The broad spectrum oncolytic activity of PV701 is due to tumour-specific defects in the interferon antiviral response. Prior study [J Clin Oncol 2002; 20: 2251-2266] has shown that IV PV701 can be administered safely to patients (6 doses over a 2 week period q 21 days). Following a 1st dose of 12 billion plaque-forming units (BPFU)/m^2, desensitization to the adverse event profile was observed for the subsequent 5 doses. This allowed the repeat dose to be 10-fold higher than the 1st dose (120 vs. 12 BPU/m^2). Flu-like symptoms were common after the 1st dose, decreasing in severity and frequency with subsequent doses. In an effort to further improve first dose tolerability, the current phase I trial evaluated a 2-dose desensitization methodology. This approach uses intrapatient dose escalations from 1 BPFU/m^2 to 12 BPFU/m^2 to further reduce 1st-dose toxicity and adverse events of subsequent higher doses of up to 120 BPFU/m^2.
Methods: Adults with advanced, incurable solid tumours, good performance status and adequate end-organ function were enrolled. PV701 was given IV over 30 minutes, 6 times in 2 weeks, cycled q 21 days. 4 dose levels were studied. In each cohort, the 1st and 2nd doses were 1 and 12 BPFU/m^2, respectively. Doses 3-6 were constant in each patient (pt), but escalated by cohort: 24, 48, 96, 120 BPFU/m^2. DLT was defined as any drug-related toxicity of grade 3/4 seen during cycle 1. Pts were assessed for response after cycle 2; those benefiting could continue on an extension protocol.
Results: Thirteen pts have been enrolled to date (7 males; median age 58; 5 colorectal; 2 each breast, sarcoma, ovary; 1 each NSCLC, anal). First dose toxicity consisted of flu-like symptoms lasting < 72 hours, all grade 2 or less, and less severe than that seen with the previous phase I study. No DLTs have been observed to date. Median number of cycles delivered = 2 (range <1 - 8). Of 10 pts currently evaluable for response: SD = 5; PD = 5. Analysis of antibody response is ongoing.
Conclusions: Two-step desensitization of IV PV701 is well-tolerated with an improved safety profile compared to the previous phase I trial. Enrollment to dose level 4 (six doses at 1/12/120/120/120/120 billion PFU/m^2 per cycle) continues. This novel intravenous dosing methodology will be utilized in planned phase II studies of PV701.

Drug resistance and modifiers

517

Peptide PNC-28 of the p53 binding domain to mdm-2 is a potent inhibitor of growth of carcinoma cells in a novel *in vivo* model of pancreatic carcinoma

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Pancreatic cancer remains one of the most lethal cancers causing death of >30,000 people per year in the US alone with a similar number of new cases diagnosed every year. Other than radical surgery, frequently not a viable option for the patient, there is only little that medical practice can do to prolong significantly a patient's life. Pancreatic cancer is unique in that in >90% of the tumors single point mutations have been identified in the genes of the ras proto-oncogene family as well as mutations in the p53 anti-oncogene in >75% of the tumors. Using conformational analysis on the p53-protein and its interaction with its regulatory protein mdm-2 we have identified peptides from the mdm-2 binding domain of p53 (residues 12-26) that upon introduction into tumor cells cause rapid necrosis in several different tumors including the novel pancreatic cancer cell lines BMRPA1.TUC3 and BMRAP1.NNK. In contrast, the same p53 peptides were not cytotoxic for normal differentiated pancreatic cells, BMRPA1, and did not inhibit the differentiation of human hematopoietic stem cells (PNAS 98:12438-12443, 2001). During synthesis, the peptides were linked to a penetratin leader enabling their direct entry into the cells' cytoplasm. We have now examined the effect of one of the p53-penetratin peptides, PNC-28, in a novel pancreatic carcinoma model established by the xeno-transplantation of BMRPA1.TUC3 cells into Nu/Nu mice. In these mice the tumor tissue displayed a typical desmoplastic reaction, invasive metastatic growth into the surrounding tissue and metastasis to the lungs, liver, pancreas and intestine. Examining the PNC-28 peptide effect on this tumor, we have found that (a) when applied 5ds prior to a subcutaneous or intraperitoneal tumor cell implantation, PNC-28 blocked growth of BMRPA1.TUC3 cells in all but 1 of the 9 mice treated (1/9);(b) PNC-28 arrested tumor growth (0/10) and prevented distant metastases when treatment of the transplanted Nu/Nu mice occurred within 24 h of tumor cell transplantation;(c) PNC-28 exerted its effect irrespective of having been injected either at or distant to the site of tumor implantation. In contrast, simultaneous treatment of tumor-laden Nu/Nu mice with a penetratin-control peptide (PNC-29)neither slowed tumor growth nor delayed metastases. Together with the *in vitro* studies the present results strongly suggest that PNC-28 may provide an effective treatment of pancreatic cancer. Supported by the Lustgarten Foundation.

518

Retained sensitivity to brostallicin after loss of DNA mismatch repair

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Defects in DNA mismatch repair (MMR) are associated with predisposition to tumorigenesis and with drug resistance owing to high mutation rates and failure to engage DNA-damage-induced apoptosis. DNA minor groove binders (MGBs) are a class of anticancer agents highly effective in a variety of human cancers. Due to their mode of action, MGBs agents may be targets for MMR induced resistance. This study was aimed at investigating the effect of loss of MMR on the sensitivity to brostallicin (PNU-166196), a novel synthetic alpha-bromoacrylic, second generation DNA MGB, using a proliferation assay (MTT) and the clonogenic assay. We report that MLH1-deficient HCT116 parental colorectal adenocarcinoma cells were 2-fold more sensitive to the antiproliferative effect of brostallicin than the MLH1-proficient HCT116+ch3 counterpart, but that MLH1-deficient cells were as sensitive to the clonogenic survival as the MLH1-proficient cells. Likewise, MSH2-deficient HEC59 parental endometrial adenocarcinoma cells were as sensitive to the clonogenic survival to brostallicin treatment as the MSH2-proficient HEC59+ch2 counterpart. In addition, p53-deficient mouse fibroblasts lacking PMS2 exhibited a 2-fold higher sensitivity to brostallicin than PMS2-proficient cells in the MTT assay, but the clonogenic assay did not reveal any difference in sensitivity to this agent between PMS2-deficient and PMS2-proficient cells. These data demonstrate that, unlike to other MGBs, MMR-deficient cells retain their sensitivity to brostallicin, indicating that brostallicin-induced cytotoxicity does not depend on functional MMR. These findings suggest testing brostallicin in the treatment of MMR-defective tumors.

519

Phase I study to determine the safety of MS209 in combination with docetaxel in patients with solid progressive tumor

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MS209 (MS) is an oral dihydroquinoline derivative, which binds directly to P-glycoprotein, and belongs to MDR inhibitors. This new compound is tested in a phase I study in combination with docetaxel (D). D is administered as a 1-hour infusion every 3 weeks, with corticosteroid premedication. At cycle 1, D is administered alone and for further cycles MS is given 30 minutes before D. The dose escalation scheme follows a modified Fibonacci model with 6 steps (D from 60 to 100 mg/m^2 and MS from 300 to 1200 mg/body). Three patients are registered by dose level; the cohort size can be extended up to 6 patients in case of dose-limiting toxicity (DLT). DLT is defined as neutropenia grade (G) 4 for more than 7 days, thrombocytopenia G4, febrile neutropenia and any G3-4 non-hematological toxicity except alopecia, nausea-vomiting - and was evaluated during cycle 2. PK samples are collected during the first 24 hours at cycle 1 and 2. As of May 2002, 26