Other mild/moderate toxic manifestations were pyrexia, anorexia, and fatigue. No toxic deaths occurred during the trial.
In conclusion, MMDX shows good activity against HCC and is well tolerated, the majority of the events being of severity Gr 1 or 2 and reversible in all cases. Altogether, the objective responses observed in Ph I-II studies by IHA, indicate an overall RR of 24.5% (13 PRs/53 HCC pts; 95% c.i.; 13.7–38.3%), confirming a significant activity of MMDX in this disease. A manageable safety profile coupled with a wide therapeutic index (objective responses obtained also at 200 mcg/m^2) characterizes MMDX as a suitable compound for the IHA management of liver cancer.

471 POSTER

In vitro and in vivo antitumor activity of nemorubicin metabolites

C. Geroni[1], R. Battaglia[2], M. Floreani[3], D. Ballinari[1], A. Marsiglio[1], L. Quintieri[3]. [1]*Nerviano Medical Science S.R.L., Biology Dept, Nerviano, Italy;* [2]*Nerviano Medical Science, Global Drug Metabolism Dept, Nerviano, Italy;* [3]*University of Padua, Pharmacology and Anesthesiology Dept, Padova, Italy*

Nemorubicin (MMDX) is a doxorubicin (DX) derivative currently in phase II/III clinical trials for the treatment of hepatocellular carcinoma. As for other anthracyclines, the major metabolic pathway for MMDX, is the stereoselective reduction of the side chain C_{13}-carbonyl group, yielding the corresponding alcohol derivative, MMDXol. In terms of plasma AUC the MMDXolo/MMDX ratio was about 0.1 in the rat, 3 in the dog, 0.7–1 in the monkey and 0.1 in humans. Moreover, MMDX undergoes hepatic oxidation by cytochrome P4503A4 to a more cytotoxic metabolite, PNU-159682, which has different DNA-interacting properties than MMDX.
In order to further characterize the pharmacological profile of MMDX, the two metabolites, MMDXol and PNU-159682 were tested in vitro toward a panel of drug-resistant cell lines and in vivo on murine and human tumor models.
Exponentially growing tumor cells resistant to DX (L1210/DX and LoVo/DX) or topoisomerase (topo) II inhibitors (CEM/VM-1) or topo I inhibitors (L1210/CPT and L1210/9-AC) and their sensitive sublines, were treated in vitro with the two metabolites. Efficacy was expressed as ratio between the IC_{50} on resistant and sensitive cells (resistance index; RI). The in vivo antitumor efficacy and the tolerability of MMDX and its metabolites were tested on murine leukemias (L1210, P388 and P388/DX) or on human mammary carcinoma xenografts (MX-1).
MMDXolo was 3–10 times less cytotoxic and PNU-159682 was 1300–4000 times more cytotoxic than MMDX in vitro. On DX resistant cells, MMDX, MMDXol and PNU-159682 were active, with RI of 2.6, 4 and 4, respectively, on L1210/DX and 1, 4 and 1, respectively, on LoVo/DX cells. Unlike other anthracyclines, MMDX does not interfere with DNA topo II functions and is effective on CEM/VM-1 cells. Both the tested metabolites overcame, as the parent drug, topo II-mediated resistance. The behavior of these compounds on topo I resistant cells was very interesting. MMDX (RI 148 and 80, respectively) and MMDXol (RI 12 and 7.5, respectively) were not effective while PNU-159682 shows activity with RI of 1 on both cell lines. In vivo, MMDXol showed activity comparable to that of MMDX on both P388 and P388/DX leukemias (ILS% 75 and 72, respectively) but at doses 14 times higher. PNU-159682 was as active as MMDX on L1210 murine leukemia but at doses 10 times lower. MMDX, MMDXol and PNU-159682 show a comparable good efficacy on MX-1 (99% tumor growth inhibition and cured mice).

472 POSTER

Assessment of the therapeutic activity and dose optimization for the anthracycline RTA 744 (WP744) using a xenograph model

N. Thapar[1], C. Meyer[2], W. Huff[2], K. Culotta[1], I. Fokt[3], W. Priebe[3], T. Madden[1,3], M. Johansen[1,3]. [1]*University of Texas M.D. Anderson Cancer Center, Pharmaceutical Development Center, Houston, TX, USA;* [2]*Reata Discovery, Inc, Dallas, TX, USA;* [3]*University of Texas M.D. Anderson Cancer Center, Experimental Therapeutics, Houston, TX, USA*

RTA 744, a 4′-O benzyl-modified anthracycline possessing superior activity against most tumor types when compared to doxorubicin, is now undergoing preclinical development. This compound differs from currently available anthracyclines by its ability to circumvent MDR1 and MRP1-mediated cellular efflux and enhanced activity in cells overexpressing Bcl-2 and its homolog Bcl-X_L. We previously described its pharmacology and toxicology in vivo and are now optimizing dose and scheduling using a human breast tumor xenograft model. Nude (nu/nu) mice (F, ~20 g) were subcutaneously implanted with MDA-MB-231 tumor cells and treatment was initiated when tumors reached 60–75 mg, approximately 10–15 days following implantation. Treatment groups (8 mice/group) were administered IP doses ranging from 5–25 mg/kg/dose using either a twice weekly (2XW) or a daily × 5 (QDX5) dosage regimen. During treatment courses animals were monitored for body mass changes, tumor growth, and toxicity. Tumor measurements were obtained twice weekly and converted to tumor weight using a standard formula. Upon termination, mice were weighed, sacrificed and the tumors harvested. Mean tumor weight per group was used for comparison between cohorts with tumor growth inhibition (TGI) calculated for each group.
In groups receiving 5 and 6 mg/kg on a QDX5 schedule mean weight loss was 8.3% and 10.4%, respectively, at the end of the treatment course. Mean TGI was 49% in the 5 mg/kg QDX5 group and 63% in the 6 mg/kg QDX5 group. The groups receiving 15 and 25 mg/kg 2XW experienced weight loss of 15% and 30% and TGI of 61% and 71% respectively. At an equivalent cumulative weekly dose, increased TGI and less toxicity (evidenced by weight loss) was observed in the QDX5 versus the 2XW schedule. To refine the RTA 744 MTD, studies were conducted in non-tumor bearing mice administered doses of 7, 8, and 9 mg/kg IP QDX5 on a repeating schedule. Increased tolerability was observed with this dose schedule; animals in the 7 mg/kg group showed an 11.2% weight loss by day 7 which was almost totally reversed by the start of course 2. Interestingly, weight recovery began immediately following the second course in the 7 mg/kg group, while weight continued to decline for an additional 9 days in the 8 mg/kg group.
These data indicate that RTA 744 is active against human breast cancer and can be optimally administered using daily dosing schedules incorporating brief rest intervals. Future studies will examine more protracted dosage regimens, utilizing brief rest periods, to further optimize efficacy and minimize toxicity.

DNA repair

473 POSTER

Poly(ADP-ribose) polymerase inhibitor, ABT-472 enhances antitumor activity of doxorubicin in human xenograft models and protects against drug-induced cardiac toxicity

I. Joseph[1], D. Ferguson[1], J. Palma[1], M. Refici[1], L. Godzicki[1], L. Rodriguez[1], D. Frost[1], S. Rosenberg[1], R. Grandel[2], W. Wernet[2]. [1]*Abbott Laboratories, Cancer Therapeutics, Abbott Park, USA;* [2]*Abbott GmbH & Co. KG, Ludwigshafen, Germany*

Poly(ADP-ribose) polymerase (PARP) is an essential DNA-damage sensing enzyme that facilitates DNA repair. Consequently, PARP may allow cancer cells to recover from chemotherapy-induced DNA damage. Inhibition of PARP (pharmacological or knockout studies) can enhance the toxicity of DNA-damaging agents. Therefore, the inhibition of PARP *in vivo* may increase the maximum therapeutic benefit of DNA-damaging chemotherapeutic agents. ABT-472 is a potent PARP inhibitor of both PARP-1 and PARP-2 enzymes (K_i, 2–2.5 nM and cellular IC_{50}, 20 nM) with a good PK profile. The ability of ABT-472 to enhance anti-tumor efficacy of doxorubicin was tested both *in vitro* and *in vivo* against the established HT-1376 human bladder carcinoma and A-253 head and neck xenografts grown in *scid* mice. *In vitro* studies demonstrated that ABT-472 increases doxorubicin sensitivity (2–3-fold) by increasing DNA strand breaks and enhancing cell death. HT-1376 tumor-bearing *scid* mice were treated with the maximally tolerated dose (MTD) of doxorubicin (0.67 mg/kg/day, i.p., for 3 cycles), ABT-472 (20.6 mg/kg/day, i.p., OMP) or the combination. The %T/C ratios on day 24 were 64, 101 and 48 and the %ILS values were 0, 0 and 64 for doxorubicin, ABT-472 and doxorubicin/ABT-472-treated groups, respectively. Efficacy of ABT-472 in combination with doxorubicin at MTD was also tested in A-253 tumor-bearing *scid* mice. The %T/C ratios on day 30 were 73, 77 and 35 and %ILS values were 21, 0 and 50 for doxorubicin (0.67 mg/kg/day, i.p., for 3 cycles), ABT-472 (10.3 mg/kg/day, i.p., OMP) and the combination group, respectively. Western blot analysis also demonstrated that ABT-472 inhibited doxorubicin-induced PAR accumulation in tumors *in vivo*. These studies demonstrate that ABT-472 significantly enhanced efficacy of doxorubicin in these xenograft models shown to be resistant to the drug at its MTD. ABT-472 alone did not show single agent anti-tumor activity. The combination of doxorubicin and ABT-472 was well tolerated. One of the major toxicities of the anthracycline class of drugs is cardiac toxicity (cardiomyopathy resulting from free radical-induced damage). Interestingly, ABT-472 protects against doxorubicin-induced acute cardiac damage indicated by survival of mice and inhibition of serum levels of troponin I and creatine kinase, markers for cardiac damage. Collectively, these studies demonstrate that ABT-472 significantly enhances the anti-tumor efficacy of doxorubicin in pre-clinical xenograft models by inhibiting doxorubicin-induced PAR accumulation. Moreover, not only is ABT-472 well tolerated in combination with doxorubicin, but ABT-472 also protects against doxorubicin-induced acute cardiac toxicity.