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host-dependent processes promoting cancer cell growth. ZD1839 showed an IC_{50} of 10.3-35.0 ng/ml for EGFR isolated from A431 vulval squamous carcinoma. This study evaluated the pharmacokinetics of ZD1839 following oral administration of single (50mg) and repeated (50-700 mg/day) doses in pts (n=6-10/group) with advanced malignancies. 57 pts (median age 55 years, range 28-75) provided blood samples included in the pharmacokinetic analysis. Blood samples obtained up to 6 days after the single 50 mg dose, and at intervals during and for 6 days after the multiple-dose phase, were analysed by HPLC. Following the single 50 mg dose, maximum plasma drug concentrations (mean 45 ng/ml; range 26.9-62.1 ng/ml) occurred 1-5h post-dose. Concentrations declined biphasically thereafter with a mean terminal $t_{1/2}$ of 34h. Exposure (AUC_{0-24}) following single and multiple administration, though variable (up to 7-fold at each dose level) increased approximately proportionally with dose with no apparent change in terminal $t_{1/2}$. On repeated administration, steady-state was achieved by day 7, and there was a 2- to 7-fold increase in exposure (AUC_{0-24})on day 14 relative to day 1. Terminal $t_{1/2}$ appeared unaltered. Thus, ZD1839 is suitable for once-daily oral administration and potentially biologically relevant concentrations of drug are achievable at the dose levels studied. *'IRESSA' is a trademark, the property of the AstraZeneca group of companies*

#3897 PHASE I STUDY OF CCI-779,A NOVEL RAPAMYCIN ANALOG: PRELIMINARY RESULTS. Jerome Alexandre, E. Raymond, H. Depenbrock, S. Mekhaldi, E. Angevin, C. Paillet, A. Hanauske, T. Le Chevalier, B. Escudier, J. Frisch, A. Feussner, and J. P Armand, *Inst Gustave Roussy, Villejuif cedex, France, and Onkologische Tagesklinik, Genetics Institute, Munich, Germany*

CCI-779, a novel rapamycin analog displays antitumor activity without significant immunosuppression in animals models. CCI-779 was given as a weekly 30 min infusion in patients (pts) with advanced solid tumors. Dose escalations were made using the modified continuous reassessment method. 15 pts (M/F: 10/5) were treated at the doses of 7.5 (1 pt, 15.0 (2 pts), 22.5 (1 pt), 34.0 (3 pts), 45.0 (3 pts), 60.0 (2 pts), 80 (1 pt), 110 (1 pt, and 165 mg/m^2/w (1 pt). So far, no dose limiting toxicity was observed. A grade (G) 1-2 skin toxicity was observed at each dose level without any evidence of dose-effect relationship: dryness with mild itching (7 pts), eczema-like lesions (3 pts), sub-acute urticaria (1 pt), and aseptic follicles (10 pts). In the latest, skin biopsies showed folliculitis and superficial peri-capillar dermatitis. 5 pts experienced reactivation of peri-oral herpes lesions. G1-2 mucositis was observed in 9 pts. All pts receiving >8 doses experienced GI nails changes. Thrombocytopenia were observed in 4 pts treated at 34 (G3), 45 (G2), 60 (G3) and 80mg/m^2/w (G1) requiring treatment delay in 3 pts. An asymptomatic increased of triglyceridemia and cholesterolemia levels were observed in 8 and 4 pts, respectively. Decreases in testoteronemia associated with an increased levels of LH and FSH were observed in 5/6 men receiving more than 4 doses at doses >15mg/m^2/w. The immunophenotype of peripheral lymphocytes and the mitogen proliferation assays did not show significant immunosuppression. 13 pts were evaluables for efficacy: 1 partial response in a patient with a IL2-IFα resistants metastatic renal cell carcinoma treated with 15mg/m^2/w, 3 minor responses, and 5 stabilization were observed. Accrual is ongoing.

#3898 A PHASE I TRIAL OF GEMCITABINE AND RADIATION IN LOCALLY ADVANCED UNRESECTABLE CANCER OF THE PANCREAS. Laurie L Herscher, C. M Muir, G. S Kroog, J. A Cook, and J. B Mitchell, *National Cancer Inst, Bethesda, MD*

Purpose: To determine the maximum tolerated dose (MTD) and dose- limiting toxicities of gemcitabine with concurrent radiation therapy in patients with unresectable adenocarcinoma of the pancreas delivered as a 30 minute infusion once weekly. *Patients and Methods:* Patients who had locally advanced or locally recurrent unresectable pancreatic cancer were eligible. Gemcitabine was administered as a 30 minute infusion once weekly for a total of 5 cycles during the course of radiation therapy. The starting dose of gemcitabine was 350 mg/m^2. Doses were escalated by increments of 25% in successive cohorts of three patients. Radiation therapy was delivered at 180 cGy/day to a total dose of 5400-5580 cGy. *Results:* Nineteen patients were entered on this study through 3 dose levels (350–550 mg/m^2. The maximum tolerated dose was determined to be 440 mg/m^2. The dose-limiting toxicity was neutropenia and thrombocytopenia. *Conclusion:* The maximum tolerated dose of gemcitabine when administered as a 30 min infusion once weekly during radiation therapy for unresectable pancreatic cancer was determined to be 440 mg/m^2. The dose-limiting toxicity was cytopenia. Concurrent gemcitabine and radiotherapy is tolerable and may represent a basis to evolve increasingly effective chemoradiotherapy of pancreatic cancer.

RADIOBIOLOGY/RADIATION ONCOLOGY 6: Radiation Biology V: Translational Research

#3899 EFFECTS OF RADIATION DOSE AND DOSE RATE ON LYMPHOCYTE POPULATIONS. Michael J Pecaut, Radha Dutta-Roy, Michael F Moyers, Gregory A Nelson, and Daila S Gridley, *Loma Linda Univ, Loma Linda, CA, and Loma Linda Univ Med Ctr, Loma Linda, CA*

The hazards of interplanetary missions have been stressed in recent reports issued by the National Aeronautics and Space Administration and the National Research Council. Of concern is the possibility that the low-dose/low-dose rate radiation inherent to Solar Particle Events (SPE) and Galactic Cosmic Rays (GCR) may enhance tumorigenesis by immunosuppression and/or DNA damage. To address the issue of immune suppression, female C57BL/6 mice (n=85) were treated with whole-body irradiation from a ^{60}Cobalt gamma source. Animals were exposed to 0, 0.5, 1.5, and 3.0 Gy at 1 cGy/min or 80 cGy/min, and euthanized 4 days later. Splenic and peripheral blood lymphocytes underwent flow cytometric analysis with antibodies against leukocytes (CD45+), T cells (CD3+), B cells (CD19+), helper/inducer T cells (CD4+), cytotoxic T cells (CD8+), and natural killer cells (NK1.1+). There were significant dose responses in both total cell counts and population distributions. In the blood, there were significant dose responses in T cell, helper/inducer T cell, B cell, and NK cell percentages ($p < 0.001$). However, only cytotoxic T and NK cell percentages were affected by the dose rate ($p < 0.02$). Similar dose and dose rate responses were observed in the splenocyte percentages, as well as in blood and spleen lymphocyte counts. These results suggest that the doses predicted during SPEs can play a significant role in radiation-induced immunosuppression. There also appear to be differences in the ability of T, B, and NK cell populations to recover from radiation exposure. Because of these differences in population dynamics, hematopoietic, apoptotic, and trafficking mechanisms may all be involved. Studies are in progress to determine whether the immunomodulation affects tumor initiation and promotion.

#3900 RADIATION EFFECTS OF TOTAL DOSE AND DOSE RATE ON COMPONENTS OF THE IMMUNE SYSTEM. Glen M Miller, Michael J Pecaut, Melba L Andres, Erik D Zendejas, Gregory A Nelson, and Daila S Gridley, *Loma Linda Univ, Loma Linda, CA, and Loma Linda Univ Sch of Medicine, Loma Linda, CA*

Interest in radiation-induced carcinogenesis has progressed as increased numbers of humans are exposed to radiation in various environmental, occupational, and therapeutic settings. Exposure to radiation can greatly modify immunological status and increase risk for cancer. In the present study, C57BL/6 female mice (n=85) were exposed to 0.5, 1.5, and 3.0 Gy total dose of whole body gamma radiation from a ^{60}Cobalt source at a low dose rate (1 cGy/min) and a high dose rate (80 cGy/min). Four days post-exposure, all mice were euthanized to analyze immmunological components for a variety of proliferative and functional properties. A decline in spleen and thymus mass strongly correlated with total dose delivered. Similarly, leukocyte counts in both the blood and spleen were inversely proportional to total dose ($p<0.001$) but independent of dose rate. In contrast, spontaneous blastogenesis results showed a directly proportional dose response. Dose and dose rate did not alter splenocyte activation by PHA or ConA, T-cell mitogens. However, splenocyte response to the B-cell mitogen, LPS, was negatively correlated with dose ($p<0.001$), independent of dose rate. Regarding cytokine production by splenocytes, IL-2 concentrations decreased as the total radiation dose increased. Cumulatively, these data suggest that protein synthesis of T-cells is affected by dose of radiation, as evidenced by IL-2 secretion, while DNA synthesis is unaffected within the same exposures. In summary, the data showed that immune components involved in tumor resistance, although highly affected by total dose, are not influenced by dose rate in these measures. Additional studies are in progress to determine long term effects of radiation exposure on susceptibility to tumorigenesis.

#3901 GENOTYPE/PHENOTYPE CORRELATIONS IN RADIATION-INDUCED PAPILLARY THYROID CARCINOMAS: THE CHERNOBYL PARADIGM. Hartmut M Rabes, S. Klugbauer, D. Hoelzel, E. Lengfelder, and E. P Demidchik, *Thyroid Cancer Ctr, Minsk, Belarus, and Univ of Munich, Munich, Germany*

The incidence of papillary thyroid carcinomas (PTC) increased in children exposed to radioactice fallout after the Chernobyl reactor accident. An analysis of 191 cases revealed various types of RET rearrangements (H4/RET, PTC1; ELE1/RET, PTC3; GOLGA5/RET, PTC5; HTIF/RET, PTC6; RFG7/RET, PTC7) with different prevalence and a few NTRK1 rearrangements. RET rearrangement-positive PTC develop rapidly, with a significantly higher prevalence of PTC3 at short intervals after irradiation. At longer latency, the prevalence of rearrangements declines with a shift from PTC3 to PTC1. The type of rearrangement is independent of age at radiation. However, the highest prevalence of PTC3 was found, irrespective of age, in the most heavily contaminated parts of Belarus. RET rearrangement is connected to a more advanced pT and pN category. In ELE1/RET tumors the solid variant of the papillary carcinoma predominates, while H4/RET tumors display more frequently the typical papillary pattern. The spectrum of radiation-induced gene rearrangements in the cohort of post-Chernobyl PTC from radiation-exposed children provides clues to phenotypes and bears implications for tumor biology and clinical course.

#3902 MALDI-MASS SPECTROMETRY ANALYSIS OF NOVEL RADIATION-INDUCED PROTEINS IN TUMORS AND HUMAN ENDOTHELIAL CELLS. M. Stoeckli, P. Chaurand, Elaine Sierra-Rivera, G. Cunningham, R. Caprioli, and D. E Callahan, *Vanderbilt Univ Sch of Medicine, Nashville, TN*

Tumor development and expansion requires a well-defined vascular supply to provide the tumor with necessary nutrients. Tumor blood vessels respond differ-