Friday

CANCER AND PLATELETS

EFFECT OF ANTICOAGULANT TREATMENT WITH RA-233 (MOPIDAMOLE) ON SURVIVAL IN BRONCHIAL CANCER. B. Schneider (1), C. Geser (2), W. Feuerer (2). Institute for Biometrics: Medizinische Hochschule Hannover, Germany (1), Dr. Karl Thomae GmbH, Medical Division, Biberach on der Riß, Germany (2).

RA-233 (mopidamole) is a phosphodiesterase inhibitor that has been shown previously to limit progression of malignancy in certain experimental animal models and in pilot studies in humans. To test its therapeutic effect a multicenter double blind controlled clinical trial was performed from 1982-1986 with patients suffering from (non small-cell) bronchial cancer. 7 centers participated and the data of 270 patients (147 treated with placebo and 123 with RA-233) could be analyzed. Median treatment time was 18 months, median observation time 21 months. With RA-233 treatment survival could be increased significantly (Savage-paper; p = 0.05 (one sided)) compared to placebo treatment (mean survival time in the RA-233 group 1080 days, in the placebo group 960 days). Cox-analysis showed a significant reduction of the hazard function to 0.6 by RA-233 treatment compared with placebo. As additional significant influence factors of the hazard function, the postsurgical TNM-class and the histological type could be revealed. Patients from stage T1 or T2 and N0 survived significantly longer than patients with other TNM-stage. But there is no interaction between treatment and TNM-class; i.e. RA-233 effect is in all TNM-stages similar. In contrast to survival metastasis-frequency and metastasis-free interval could not be influenced by RA-233.

EFFECT OF RA-233 (MOPIDAMOLE) ON SURVIVAL IN CARCINOMA OF THE LUNG AND COLON. FINAL REPORT OF VA COOPERATIVE STUDY U108, L.H. Zacharski (1) and T.C. Moritz (2). For the VA Cooperative Study Group on Anticoagulants and Cancer, Dartmouth Medical School and the VA Medical Center, White River Jct., VT 05001, U.S.A. (1) and the VA Cooperative Studies Program Coordinating Center, VA Medical Center, Kines, ILL 60041, U.S.A. (2).

RA-233 (mopidamole) is a phosphodiesterase inhibitor that has been shown previously to limit progression of malignancy in certain experimental animal models and in a pilot study in humans. RA-233 plus chemotherapy was compared with chemotherapy alone in a five-year double-blind trial involving 719 patients with advanced carcinoma of the lung and of the colon. No difference existed between treatment groups for a variety of demographic, clinical, and laboratory parameters evaluated at entry to the study. There were no instances of unblinding and no patients were lost to followup. Minimum followup was 1 year. Patients ingested RA-233 or placebo for over 85% of their total survival interval and took 66% of the number of pills originally prescribed. RA-233 treatment was associated with a statistically significant prolongation of survival in patients with non-small cell lung cancer limited to one hemithorax, and also with reduction in mean plasma fibrinogen concentration, and with reduction in the incidence of bleeding episodes. RA-233 was not toxic. The favorable effects on survival could not be explained by any factor other than the RA-233 treatment. In other tumor categories tested no differences in survival were observed. These results suggest that RA-233 may be useful in the treatment of non-small cell lung cancer of limited extent (and possibly other tumor types). They also suggest that therapeutic intervention aimed at modified pathways within tumor cells might constitute an innovative investigational approach to the treatment of cancer.

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PLATELET CALCIUM MOBILIZATION

DIRECT STIMULATION OF Ca2+-ACTIVATED HUMAN PLATELET PHOSPHOLIPASE A2 BY DIACYLGLYCEROL. D. Deykin and R. M. Kramer. Boston VA Medical Center and Boston University School of Medicine, Boston, MA, U.S.A.

These studies examined the effect of diacylglycerol on Ca2+- dependent phospholipase A2 from human platelets. Phospholipase A2 was solubilized and partially purified to a stable form in the presence of octylglucoside and its enzymatic activity determined using sonicated arachidonoyl phosphatidylcholine (PC) as substrate. (Kramer RM, et al: BBA 578:394, 1986) Phospholipase A2 activity was increased when diacylglycerol was incorporated into the substrate arachidonoyl-PC. In the presence of 1 mM (29 mol %) sn-1,2-dioleoylglycerol the enzymatic activity was stimulated 0.7-fold. Exogenously added myristoyl-13-acetate diacylglycerol also enhanced phospholipase A2 activity, producing a maximal stimulation of 1.6-fold at a concentration of 25 uM. Comparative studies conducted with pancreatic, bu-venom and snake venom phospholipase A2 showed that the activity of these extracellular phospholipases towards the arachidonoyl-PC substrate was also increased by diacylglycerol, but the stimulation was less than observed for platelet phospholipase A2. We conclude that in stimulated platelets Ca2+-activated phospholipase A2 may be regulated by newly generated diacylglycerols, not only via protein kinase C-mediated events, but also directly through conformational changes imposed by the diglycerides on cellular membrane phospholipids.

REGULATION OF PLATELET RECEPTORS FOR FIBRINOGEN AND VON WILLEBRAND FACTOR BY PROTEIN KINASE C. Sheila Timmons and Jack Hawiger. New England Deaconess Hospital and Harvard Medical School, Boston, MA. 02215, USA.

Positive and negative regulation of platelet receptors for adhesive proteins, fibrinogen (F) and von Willebrand Factor (vWF) determines whether binding of these ligands will or will not take place. We have examined regulation of F and vWF binding to platelets via the glycoprotein IIb/IIIa complex in a five-year double-blind trial involving 719 patients with advanced carcinoma of the lung and of the colon. No difference existed between treatment groups for a variety of demographic, clinical, and laboratory parameters evaluated at entry to the study. There were no instances of unblinding and no patients were lost to followup. Minimum followup was 1 year. Patients ingested RA-233 or placebo for over 85% of their total survival interval and took 66% of the number of pills originally prescribed. RA-233 treatment was associated with a statistically significant prolongation of survival in patients with non-small cell lung cancer limited to one hemithorax, and also with reduction in mean plasma fibrinogen concentration, and with reduction in the incidence of bleeding episodes. RA-233 was not toxic. The favorable effects on survival could not be explained by any factor other than the RA-233 treatment. In other tumor categories tested no differences in survival were observed. These results suggest that RA-233 may be useful in the treatment of non-small cell lung cancer of limited extent (and possibly other tumor types). They also suggest that therapeutic intervention aimed at modified pathways within tumor cells might constitute an innovative investigational approach to the treatment of cancer.

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