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205 CYTOTOXICITY OF COPPER AND IRON COMPLEXES OF 5-SUBSTITUTED-2-FORMYLPYRIDINE THIOSEMICARBAZONES (HL). D. H. Petering, W. Antholine, J. M. Knight, and H. G. Petering, Department of Chemistry, University of Wisconsin-Milwaukee, Milwaukee, WI 53201 and Department of Environmental Health, University of Cincinnati, Cincinnati, OH 45219.

The cytotoxicity of metal complexes of HL against Ehrlich ascites tumor cells has been examined. Short in vitro incubation of cells and drugs followed by implantation of cells into mice and observations of tumor growth was used to assess cytotoxic effects. Using $5x10^6$ cells/ml and 2 mg/ml of the iron complexes, the following order of activities was observed, beginning with the least active complex, OH < $-OCOCH_3$ ~ $-N(CH_3)_2$ < H < $-CH_3$ ~ $-Cl$ ~ $-CF_3$. The last two complexes completely prevent tumor development over long periods. At 0.1 mg/ml copper complexes of 5-H and 5-CH_3 completely inhibit transplantation. In contrast, 2 mg/ml of the 5-H ligand has less effect than either its iron or copper complex. These results indicate that metal complexes of HL as well as parent ligands need to be examined for their antitumor properties. (Supported by NCI CA 16156.)

206 MORPHOLOGICAL MODIFICATION OF A VIRUS-INDUCED LYMPHATIC LEUKEMIA BY THYMECTOMY AND ANTILYMPHOCYTE SERUM. Steven L. Dresler, Peter J. Dawson, and A. Howard Fieldsteel. Univ. Oregon Med. Sch., Portland, Ore. 97201 and Stanford Research Inst., Menlo Park, Ca. 94025.

Since most human lymphocytic leukemias in contrast to murine leukemias possess B-cell markers, we attempted to induce with virus a murine leukemia of B-cell origin. Groups of BALB/c mice were thymectomized at 5-7 days of age, treated with antilymphocyte serum (ALS) on days 7, 8 and 9 and inoculated on day 8 with lymphatic leukemia virus (LLV-F) isolated from Friend virus. Control animals were either thymectomized and given ALS (and no virus) or were sham-thymectomized and inoculated with virus. Control animals developed lymphocytic leukemia involving thymus, periarteriolar sheaths of spleen, portal areas of liver, lymph nodes and bone marrow. Immunofluorescence showed θ antigen on leukemic lymphocytes and absence of immunoglobulins. In thymectomized mice, leukemia developed later and involved the splenic red pulp, hepatic sinusoids and bone marrow. Lymph nodes and periarteriolar sheaths of the spleen were spared. Cytologically the cells were different and lacked both T and B cell determinants. Possible explanations are the transformation of a different clone of lymphocytes by LLV-F, the unmasking of trace amounts of Friend virus or the presence of another leukemia virus.

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207 PHASE I STUDY OF 5-AZACYTIDINE USING 24 HRS CONTINUOUS INFUSION FOR 5 DAYS. Pavel L. Lomen, V. K. Vaitkevicius, and Michael K. Samson. Dept. of Oncology, Wayne State University, Detroit, Mich. 48201

The biological and antitumor activity of 5-azacytidine (5-azaCR) has been well demonstrated in the past. The drug at present is thought by most to be primarily cell cycle phase specific. This study was designed to eliminate undesirable side effects occurring with a bolus dose and to confirm the recent findings of relative stability of 5-azaCR's solution with preserved biological and antitumor activity. In the study we determined that 150 mg/m^2/day given as a 120 hr continuous intravenous infusion, repeated at 28 day intervals produced safe, manageable, and reproducible toxicity. The drug was freshly prepared at 4 hr intervals. Eleven courses were administered to 6 patients at this dose level. No patient experienced nausea or vomiting. Leukopenia was the major toxicity. Mean nadir of WBC was 2.6×10^3 (range 0.7-6.1). Day 17 was the mean day to nadir with recovery occurring within 2-13 days. In only 3 courses was thrombocytopenia ($7-92 \times 10^3$) produced. In two patients multiple samples of plasma and urine were analyzed by microbiologic assay. There was no 5-azaCR detected in the plasma samples. In 24 hr urine collections, there was 0.89% and 0.74% of free azacytidine detected. Antitumor activity was demonstrated in one patient with colon cancer and another with American Burkitt's lymphoma. Analysis of this study confirmed our expectations and pointed out some new aspects of 5-azaCR metabolism.

208 MECHANISM OF 5-FLUOROURIDINE TOXICITY IN NOVIKOFF HEPATOMA CELLS. David S. Wilkinson and Jeanne Crumley. University of South Florida, Tampa, Florida 33620.

Several of the fluorinated pyrimidines have the ability to inhibit rRNA maturation. This effect appears to be a significant factor in the cytotoxicity of 5-fluorouridine (FUrd) in Novikoff hepatoma cells. The incorporation of labeled precursors into mature 18S and 28S rRNA is completely inhibited by the simultaneous addition of $1x10^{-4}$M FUrd, whereas the cells must be preincubated with this drug for 2 hrs before comparable inhibition of DNA synthesis occurs. When cells are incubated with $1x10^{-5}$M FUrd for one hr, washed, resuspended in fresh medium for 1 hr and then exposed to [^{3}H] guanosine for 90 min, one finds little or no incorporation of precursor into mature 18S or 28S rRNA. Under similar conditions, there is very little inhibition of DNA synthesis. Cells exposed to $1x10^{-5}$M FUrd for one hr and then allowed to incubate for one hr in analog-free media do not grow when subcultured into standard media. The addition of $1x10^{-4}$M uridine (Urd) during analog exposure prevents most of the growth inhibition, whereas the addition of $1x10^{-4}$M thymidine (Thd) has little effect. Thd, which can prevent the inhibition of DNA synthesis by FUrd, does not prevent the inhibition of rRNA maturation. However, Urd, which blocks the growth inhibitory effects of FUrd, also blocks the inhibition of rRNA maturation. (Supported by DRG-1220 and ACS F73FS-2).