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C-114*

...TERED CENTRAL-NERVOUS-SYSTEM (CNS) PHARMACOLOGY OF ...THOTREXATE (MTX) IN ACUTE LYMPHOBLASTIC LEUKEMIA (ALL): ...NOTHER SIGN OF CNS RELAPSE. M. Morse, F. Balis, D. Poplack ...nd A. Bleyer. Children's Orthopedic Hospital and Medical ...Center (COHMC), Seattle. WA 98105 and Pediatric Branch, NCI, ...Bethesda, MD 20205.

Intravenous infusions of high-dose MTX (HDMTX) have been used successfully in patients (pts) with ALL to prevent and treat CNS relapse (cf. Poplack et al and Balis et al in these proceedings). In 1979-1982, CSF MTX concentrations were monitored in 60 children at COHMC with poor-prognosis ALL. These patients were enrolled on a conjoint NCI and Childrens Cancer Study Group study (NCI 77-02/CCG-191) in which the CNS prophylaxis was randomized to either HDMTX or standard therapy with cranial radiation and intrathecal MTX. HDMTX consisted of MTX 33.6 Gm/m2 IV over 24 hr and high-dose citrovorum rescue therapy initiated 12 hrs after each HDMTX infusion (Poplack et al, ibid.). In 49 pts who have had no evidence for CNS leukemia, the mean steady-state CSF:plasma MTX ratio was 0.013 (SD=0.01). In contrast, 11 pts with overt CNS leukemia had a more than ten-fold higher mean ratio of 0.157 (range: 0.013-0.844) ($p<0.01$). All pts with CSF MTX concentrations > 2 SDs above the mean either had leukemic cells in their CSF or subsequently relapsed in the CNS. In one pt, a high CSF:plasma drug ratio preceeded CNS relapse. In another pt, failure of the ratio to return to normal was associated with a short CNS remission duration. In all other pts, the CSF MTX level and the CSF:plasma ratio promptly declined to normal as CSF remission was achieved. As previously observed with intrathecal MTX, we conclude that overt CNS leukemia also increases CSF MTX concentrations during intravenous MTX therapy. An elevated CSF:plasma ratio may be useful to predict imminent CNS relapse or to verify completeness of response to therapy.

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C-115*

SCREENING FOR TOXICITY AND EXCRETION OF MUTAGENS IN POPULATIONS HANDLING CHEMOTHERAPEUTIC DRUGS. P. Tuffnell, G. DeBoer, A. Dong, C. Erlichman and M. Gannon. The Princess Margaret Hospital, Toronto, CANADA, M4X 1K9.

Published reports of detecting mutagens in the urine of persons handling chemotherapeutic drugs have caused concern. We have studied 42 drug handlers and 20 controls over a two year period. Drug handlers included pharmacists working under vertical laminar flow hoods and nurses utilizing protective clothing and a similar technique but no hood. Parameters assessed were white blood cell counts, differentials, platelet counts, hemoglobin and the mutagenicity of urine extracts in the Ames test using the two test organisms TA98 and TA100.

Blood counts every three months showed no significant difference between handlers and controls. Preliminary tests established that of drugs in common use only doxorubicin, cyclophosphamide, cisplatin, carmustine and nitrogen mustard were mutagenic. Tests of urine from patients receiving therapeutic doses of doxorubicin and cyclophosphamide suggest that 1 mg and 5 mg respectively would have to be absorbed to cause mutagenic urine. Of 434 casual urine specimens, 9 were borderline positive (1.8-2.6 times background). Four were in controls and 5 in handlers. Seventeen 24-hour specimens from handlers were non-mutagenic but 5 (29%) were toxic as were 51 of the casual urines (12%). Some toxicity was due to tetracycline but most was unexplained. Toxicity, the limited range of drugs that can be detected by the mutagenicity, lack of specificity, sensitivity and variability of urinary excretion, limit the usefulness of the Ames test for screening for environmental exposure to chemotherapeutic drugs.

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C-116*

EFFECTS OF VERAPAMIL ON DOXORU... DIFFERENTIAL SENSITIZATION OF HUM... SELECTED IN VITRO VS. IN VIVO. W. G. ... D. M. Bauer, R. A. Newman, and B. I. Sikic. ... School of Medicine, Stanford, CA 94305 and ... Burlington, VT 05405.

The calcium antagonist verapamil (VPM) ... the cytotoxicity of doxorubicin (DOX) in mu... leukemia cell lines resistant to DOX. We have ... of VPM on the cytotoxicity of DOX in D... of the human sarcoma cell line MES-SA. T... 100-fold resistant to DOX and cross-resist... (ACT-D), daunorubicin (DNR), mitoxantrone ... (VP-16), mitomycin (MMC), melphalan (ML... and vinblastine (VLB). DOX cytotoxicity ... by VPM (1 and 10 μg/ml) in $Dx_{5.0}$ but not ... 0.1 μg/ml was ineffective in enhancing D... 10 μg/ml was no more effective than 1 μg/ml. ... the cytotoxicity of DNR, ACT-D, VP-16 and ... did not, however, affect the cytotoxicity o... or VLB in $Dx_{5.0}$. VPM did not alter ^{14}C-... either $Dx_{5.0}$ or MES-SA.

We have also examined the effect of VPM ... of DOX in cells from human solid tumors. ... and 5 ovarian carcinomas were selected be... resistance to DOX in soft agar clonal assay... to DOX and VPM (3 μg/ml) revealed no e... in any of the 6 tumor samples compared to D... carcinoma cell lines, 1 resistant and 1 sen... failed to show enhanced DOX cytotoxicity by ...

Thus, VPM may enhance the cytotoxicity ... human cell lines specifically selected for DO... in a small number of DOX resistant human ... have failed to demonstrate enhanced DOX cyto...

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C-117

COAGULATION CHANGES AND PULMONARY FIBROSIS ... BLEOMYCIN TREATMENT IN ANIMALS: DIFFERENT ... FACTORS: U. Göbel[1], A. Schmitt-Gräff[2], W. ... Kries[1], H. Jürgens[1]. [1]Kinderklinik B und ... Institut der Universität, 4000 Düsseldorf...

The major adverse effect of bleomy... fibrosis. Direct damage of the pulmonary ... struction of alveolar makrophages, disse... coagulation (DIC) (Burkhardt H et al, Dru... 281-289, 1977) are discussed as pathogen... Recently it was shown in an animal model ... results in hypercoagulation and most of ... mals developed pulmonary fibrosis (Göbel ... Soc. Clin. Oncol. 2:39 (C-155), 1983). In ... role of hypercoagulation for the pathogen... fibrosis in animals treated with bleomyc... 1 to 9 years) were treated with bleomycin ... every fourth day for a total of 50 i.m. ... tional 5 beagle dogs received the same ... also in addition 250 i.U./kg body weight ... ously twice daily. The following tests w... during the treatment period and during a ... up period once bleomycin was discontinued: ... platelet aggregation with ADP, collagen, ... cetin; platelet-factor 3 release; PTT; ... tors I,II,V, and VII. The addition of ... significant prolongation of most coagul... platelet function test returned to normal ... cidence of pulmonary fibrosis was the sa... groups, where 4 dogs had developed a se... changes at autopsy. It may be concluded ... that preventing hypercoagulation result... using heparin does not prevent bleomycin ... fibrosis.

With support of the 'Ministerium f. Wis...

REINDUCTION THERAPY WITH 4'(9-ACRIDINYLAMINO) ANISIDE (AMSA) AND CYCLOCYTIDINE (CYCLO) IN ACUTE NONLYMPHOBLASTIC LEUKEMIA (ANLL). A. Pysemany, P. Rogers, L. Wolff, S. Siegel, D. Hammond. Childrens Cancer Study Group geles, CA. 90031.

an active agent for reinduction for ANLL in combination with cyclo it is effective for (Cancer Treatment Reports 67:439,1983). In (CCG-201), AMSA (75 mg/m^2 IV day 1-5) and m^2 subcutaneous day 1-7) for induction and m^2 IV day 1) and VP-16 (100 mg/m^2 IV day 1-5) for maintenance were given to 46 pts with 3/4 months-18 9/12 years). All pts were in marrow) except 2 who failed induction therapy in and cytosine arabinoside and 2 with an M_2B circulating blasts during initial maintenance 46 pts entered, 26 achieved a marrow with blasts (M_1 or M_2A) after 1 or more induction the 38 pts who completed 2 courses (adequate a complete remission: 16 entered maintenance bone marrow transplant; 2 were eligible for but refused; 1 continued on AMSA and cyclo; 1 ission of bowel perforation; and 1 relapsed 's delay in starting maintenance. Overall is greater than 50% of all pts entered on eiving an adequate trial. Duration of not yet evaluable. Toxicity included pain, vomiting, hepatic dysfunction, and ction during periods of neutropenia. Cardiac monitored in all pts; toxicity directly to AMSA was not seen. In summary, AMSA and effective combination for successful induction ANLL who fail to achieve initial remission or maintenance therapy.

CTIVE OF LONG TERM DISEASE FREE SURVIVAL FOLLATED CENTRAL NERVOUS SYSTEM (CNS) RELAPSE IN UTE LYMPHOBLASTIC LEUKEMIA (ALL). J. Ochs, L. George, H.O. Hustu and J.V. Simone. St. 's Research Hospital, Memphis, TN 38101.

ndred eighty-one childhood ALL patients have on Total Therapy Studies V-IX. CNS prophyher not given (49 patients) or consisted of ospinal (CS) or cranial (Cr) radiation plus doses of intrathecal (IT) methotrexate. 107 ated and 31 irradiated) patients have had an relapse as the first site of relapse. Of ients, 83 (77%) have had one or more addi-; 24 (23%) have had no further relapses and a median of 7 years 8 months (3 months to The following factors were analyzed for redict long term disease-free status following meningeal relapse: age at diagnosis, sex, blood cell (WBC), duration of first remis- of blast cells/mm^3 of cerebrospinal at time of CNS leukemia, number of IT injections to ectable blast cells, addition of prednisone- ulses and immediate CS radiation versus de- CS radiation following IT therapy. Only two predictive of long-term continuous disease- initial WBC $\leq$20,000 and duration of first months. Forty percent of patients with 20,000 had only the single isolated CNS re- off therapy versus 15% with initial WBC an duration of first remission was not indeitial WBC. Initial WBC should be included in and analysis of efficacy of CNS leukemia ens.

C-776

CENTRAL-NERVOUS-SYSTEM (CNS) PHARMACOLOGY OF HIGH-DOSE INTRAVENOUS METHOTREXATE (HDMTX) IN INFANTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL). A. Bleyer, G. Reaman, D. Poplack, M. Morse, J. Feusner, J. Miser and D. Hammond. Pediatric Branch, NCI, Bethesda, MD 20205 and the Childrens Cancer Study Group, Los Angeles, CA 20014.

Of 115 infants with ALL, 15% had CNS leukemia at diagnosis and 21% sustained a CNS relapse during the initial marrow remission (Reaman et. al., Proc. ASCO 2:80, 1983). Infants are also at high risk for cerebral dysfunction from cranial radiation. In the study reported by Poplack et. al. in these proceedings, children without CNS leukemia at diagnosis were randomized to receive either HDMTX or standard prophylaxis with CNS radiation and intrathecal (IT) MTX. Eight of these patients were infants <1 year of age. HDMTX (33.6 Gm/m2 IV over 24 hr and high-dose citrovorum rescue initiated at hr 36) was administered once during induction, three times times during consolidation, and once every 6 mo during maintenance. The mean CSF:plasma MTX ratio during 32 infusions in 6 infants randomized to HDMTX was 0.037, and the mean steady-state CSF MTX level was 6.9×10^{-5} M. These values were higher than corresponding values from 49 older children of 0.013 and 8.7×10^{-6} M, respectively ($p<.05$ for both). The mean steady- state plasma MTX level in the infants was 1.84×10^{-3} M, similar to that observed in older children. CSF:plasma ratios in the infants were higher during the induction HDMTX than during subsequent courses ($p_1=.05$). With a median followup of 24 months, CNS leukemia developed in one of six infants treated with HDMTX and in one of two infants treated with CNS radiation and IT MTX. CSF levels are more prolonged with HDMTX than with IT MTX, and as observed in this study, are higher in infants than in older children. HDMTX may be a desirable alternative to cranial radiation - especially in children at greatest risk of CNS radiation damage.

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C-777*

CLINICAL AND BIOLOGIC FEATURES PREDICT POOR PROGNOSIS IN ADOLESCENT ACUTE LYMPHOCYTIC LEUKEMIA (ALL). J. Pullen, W. Crist, J. Boyett, J. Falletta, J. van Eys, M. Borowitz, J. Jackson, B. Dowell, C. Russell, F. Quddus, A. Ragab and T. Vietti for the Pediatric Oncology Group.

Analyses of remission induction rates for 1018 children 1.5 to 10 years of age (Group [Grp] 1) and 250 children $\geq$10 years of age (Grp 2) with ALL and of duration of continuous complete remission (CCR) for 542 in Grp 1 and 132 in Grp 2 revealed Grp 2 to be significantly inferior in both measures of outcome ($p<.001$ and $p<.001$). To examine potential clinical and biologic reasons for the poorer prognosis of older children with ALL, the following presenting features were compared within subsets of the 2 grps: sex, race, hepatosplenomegaly, lymphadenopathy, mediastinal mass (MM), WBC, platelet count, hemoglobin (hb), and immunoglobulin levels, as well as blast cell immunophenotype distribution (T; B; pre-B; or non T, non B, non pre-B), common ALL antigen (CALLA)$^+$, peanut agglutinin receptor$^+$, complement receptor$^+$, FAB classification, PAS$^+$, acid phosphatase (AP)$^+$, glucocorticoid receptor levels, and cytogenetic features. Grp 2 patients (pts) had a higher incidence of the unfavorable phenotypes of pre-B and T-cell ALL ($p<.01$); MM ($p<.001$); high WBC ($p<.001$); high hb ($p<.001$); AP$^+$ ($p<.001$); PAS$^-$ ($p<.001$); CALLA$^-$ ($p<.001$); and poor risk cytogenetic features (hypo- and pseudo-diploidy) [$p<.01$]). Within the non T, non B, non pre-B phenotype, Grp 2 pts had: more boys ($p<.02$), more pts with L_2 FAB morphology ($p<.01$), but no difference in incidence of CALLA$^-$. CCR duration was significantly shorter for Grp 2 pts as compared to Grp 1 within the non T, non B, non pre-B grp ($p<.001$), but not within the pre-B or T grps. We conclude that adolescent pts have a high incidence of unfavorable prognostic factors, predicting the poorer outcome of Grp 2 as compared to Grp 1. However, within pre-B and T ALL, both age grps fared poorly, demonstrating the overriding prognostic significance of immunophenotype.