1.

IMMUNOMODULATION OF IMMUNESUPPRESSED CHILDREN WITH CANCER BY THYMIC HORMONE (THF). R. Zaizov, I.J. Cohen, C. Kaplinsky, A. Dvir, R. Vogel, B. Shohat, M. Pecht and N. Trainin. Pediatric Hematology Oncology, Beilinson Medical Center and Sackler School of Medicine, Tel-Aviv University and the Weizmann Institute of Science, Rehovot, Israel.

Thymic Hormone, THF, was administered to children with various malignant diseases who developed severe impaired cell mediated immunity (CMI) following intensive chemotherapy and/or radiotherapy. The children were treated either for disseminated Varicella Zoster infection, recurrent Herpes Simplex, severe interstitial pneumonitis, extreme lymphopenia, or in combination with chemotherapy in those with acute myelogenous leukemia. CMI parameters, including E rosettes, response to mitogens, GVHR, in vivo delayed hypersensitivity reaction, subpopulations of T lymphocytes by monoclonal antibodies and NK activity were determined prior, during and following THF therapy. THF induced a significant proliferation of lymphocytes restoration of CMI, including increase in helper and cytotoxic T cells as well as NK activity. The CMI restoration manifested by clinical improvement and recovery in those patients with severe viral infection and pneumonitis. The potent immunopotentiation effect of THF offers clinical therapeutic applications for immunesuppressed patients with cancer.

2.

IN VITRO AND IN VIVO EFFECTS OF SYNTHETIC FACTEUR THYMIQUE SERIQUE (FTS) ON T CELL MARKERS AND FUNCTIONS IN ALLOGENEIC MARROW TRANSPLANT RECIPIENTS. P. BORDIGONI[1], MC BENE [3], M. DONNER [4], C. JANOT [2], G. FAURE [3], M. DARDENNE [5], J DUHEILLE[2], D. OLIVE [1]. Pédiatrie A[1], C. Transfusion Sang[2], Labo. Immunologie [3], U. Inserm 95-NANCY [4], U. Inserm 25 - Hôp. Necker, PARIS [5] - F R A N C E

Disturbances of peripheral blood lymphocytes (PBL) T markers and functions follow bone marrow transplantation (BMT), and make these cells responsive to thymic factors. PBL from 9 children were studied after BMT, realized in complete remission : 8 acute leukemias (6 ALL, 1 AML, 1 ML) ; 1 Hodgkin's disease. BMT was performed with allogeneic marrow (genoidentity in 7 cases), after preparation with ablative chemo-radiotherapy. After grafting, low dose methotrexate was given for 15 weeks to prevent GVH. PBL markers and functions were studied before and after in vitro treatment with FTS at time intervals between days 20 and 55, while serum FTS levels still were markedly decreased. Number of OKT 3 + cells doubled after 2 hr. incubation with FTS at 37° C (test performed at 20). No significant increment of NK cells activity was observed after 1 hr. uncubation with FTS (cytotoxicity assay with human myeloid line K 562 as target) except in one case. 18 hr. incubation with FTS induced a significant improvement of PBL's response to mitogens (Con A, PHA).

Results of this report (the first one based on biological grounds) suggest a therapeutic use of FTS in the follow up of marrow transplant recipients. Preliminary results after in vivo treatment of 3 patients show that T. cell markers increase within 15 days, in a manner similar to what is observed in vitro. No induction or aggravation of GVH was observed.

3.

IMMUNOTHERAPY WITH THYMIC HORMONE IN PATIENTS WITH ADVANCED NEUROBLASTOMA. C.Rosanda, G.Calculli, M.Carli, L.Cordero di Montezemolo, A.Mancini, G.Pastore, C.Pianca, A.Russo, B.De Bernardi for the Italian Cooperative Group for Neuroblastoma

A thymic hormone preparation (TP_1, Serono) endowed with immunostimulating activity, has been added to "standard" chemotherapy for Neuroblastoma (NB) in advanced stages, with the aim of a) reducing susceptibility and severity of intercurrent infections, b) prolonging clinical remission and survival. Therapeutic regimen consisted of cycles of cyclophosphamide and doxorubicin. In the period March 1980-January 1982, 77 patients were enrolled in this study, 28 bearing regional inoperable disease, 49 with disseminated NB; 36/77 patients, selected randomly, were treated with TP_1 in the intervals between cycles of chemotherapy. Immune evaluation consisted of total, T and B count of peripheral blood lymphocytes; quantitation of serum immunoglobulin and C_3-C_4 levels; influence of "in vitro" incubation with TP_1 on T lymphocyte number; percentage of T and B lymphocytes in bone marrow; skin test reactivity to PHA and Candida. A "major" response to therapy was achieved in 16/36 cases receiving immunotherapy, and in 18/41 who did not receive it. The administration of TP_1 did not seem to significantly influence the number and severity of infectious episodes nor the immune status of patients. The "in vitro" incubation of peripheral blood lymphocytes with TP_1 did not consistently elevate T cell levels.

Detailed results of this study will be presented at the Meeting.

4.

EFFECT OF ANTI ALPHAFETOPROTEIN ANTIBODY (AAA) ON THE AFP PRODUCING HEPATOMA. J.Uchino, F.Sasaki, K.Manabe, T.Kuwahara, Y.Une, T.Inoue, Y.Hata, A.Kakita, Y.Kasai, for the First Department of Surgery, Hokkaido University School of Medicine, N-14, W-5, Sapporo, Japan.

Effect of the AAA on the growth of AFP producing hepatomas was investigated in vitro and in vivo.

MATERIALS AND METHODS) AntiAFP serum: Horses were immunized with a purified human AFP. In vitro: Viability of the human hepatoma cell CH-4 and hepatoblastoma cell Hb-3 was examined by the Trypan blue dye exclusion method, in the microtest plate II, containing 0.3 ml of the medium TC-199 with various consentration of AAA. In vivo: Human hepatoma (Hc-4), serially transplanted in the nude mice (1), rat ascites tumor AH-66 inoculated in the rat liver (2) and into the rat portal vein (3). AAA was administrated intraperitoneally, intrahepatic arterially and into the tumor tissue at the time of implantation and/or during the growth of the tumor.

RESULTS) The concentration dependent cell growth inhibition was clearly demonstrated. In the high AFP producing cell line growth curves were flat and descending. The doubling time was elongated in the intratumor injection group. The tumor sizes were significantly smaller than those of the control, especially in the early period of the administration. The tumor less than 100 mm3 significantly decreased. AFP levels of the tumor tissue and serum remarkably decreased especially in the high AFP producing groups. The mean survival time was significantly prolonged in the group 3.

CONCLUSION) AAA has growth inhibitory effects on the AFP producing tumors and decreases AFP production of the tumor tissue.

5.

SERUM AND CEREBROSPINAL FLUID (CSF) PHARMACOKINETICS OF RECOMBINANT LEUCOCYTE A INTERFERON (IFLrA) IN MONKEYS. R. Riccardi, M.J. Kramer, P.W. Trown, A.S. Levine, and D.G. Poplack; Pediatric Oncology Branch, NCI, Bethesda, MD 20205 and Hoffmann-LaRoche, Inc., Nutley, NJ 07110.

We investigated the serum and CSF pharmacokinetics of IFLrA in Rhesus monkeys following intravenous (IV), intramuscular (IM), and intraventricular (IT) administration. Animals with subcutaneously implanted reservoirs were utilized for these studies. Following IV and IM injections of 2.5×10^6 U/kg, serial serum samples were taken up to 12 hrs. After IV administration serum levels of about 3.0×10^4 U/ml were achieved at 2 mins and declined rapidly, with α and β half-life of about 25 ± 4 mins and 180 ± 60 mins (mean ± S.E.) respectively. Following administration of identical doses of IM IFLrA, serum levels peaked at 4 hrs. A considerable variability in IFLrA serum levels achieved following IM administration in the different experiments was noted. Transient fever was the only toxicity observed following both IV and IM administration. Negligible amounts of IFLrA were measured in the CSF following systemic administration. Following IT administration of 1×10^6 U of IFLrA, CSF levels declined with a mean α and β half-life of about 1.7 and 5.4 hrs respectively. Moderate pleocytosis (<200 cell/mm^3) and transient fever were the only toxicities observed following IT administration. In summary, there is considerable variability in IFLrA serum levels following systemic administration; only a fraction of circulating IFLrA penetrates into the CSF following systemic administration; sustained CSF IFLrA levels can be achieved following IT administration; and no major toxicity was observed following the three different routes of administration. Although the relationship between IFLrA level and its biological effects is yet unknown, our data may be of value in the planning of treatment for protocols which utilize IFLrA.
