Leukaemias and Lymphomas

58 O

SUCCESSFUL ENGRAFTMENT OF T-CELL-DEPLETED HLA-INCOMPATIBLE TRANSPLANTS.

F. Aversa, A. Terenzi, A. Tabilio, A. Velardi, F. Falzetti, L. Ruggeri, Sodani P, T. Zei, C. Giannone, R. Jacucci, °Y. Reisner and *M.F. Martelli. Section of Hematology and BMT Unit University of Perugia, 06122 Perugia Italy, °Institute of Membrane Research and Biophysics, Weizmann Inst. Rehovot, 76100 Israel.

Since March 1993, 48 patients (mean age 22 years, range 2-51) with high-risk or advanced stage leukemia (14 AML, 31 ALL, 3 CML) have been transplanted. 26 were in hematological remission (5 CR I, 20 CR ≥II. 1 2nd CP of CML) and 22 (11 AML, 9 ALL, 2 BT) in chemo-resistant relapse at the time of transplant. All donors were HLA-haploidentical "three loci" incompatible family members. The first 36 patients received a conditioning regimen that included single TBI (8 Gy), 25 mg/kg rabbit ATG, 10 mg/kg thiotepa and 100 mg/kg cyclophosphamide (Cy). In the last 12 Cy was replaced by fludarabine (40 mg/m^2/day for 6 days) and thiotepa increased to 13 mg/kg. T-cell-depletion of the bone marrow and the PBPCs by the soybean agglutinin and E-rosetting technique was the sole prophylaxis for GvHD in the first 36 patients, while a CD34-selection of E-rosetted PBPCs has been used for the last 12 cases. 46 patients engrafted. GvHD occurred in 6; 9 relapsed. 18 survive, 16 event-free at a median follow-up of 12 months (range 1-33) The details of the clinical data will be presented.

59 O

THIOTEPA IMPROVES RESULTS OF T-CELL-DEPLETED BONE MARROW TRANPLANTS FOR ACUTE LEUKEMIA. A SEVEN YEAR EXPERIENCE.

Aversa F. Terenzi A. Carotti A. Felicini R. Velardi A. Ruggeri L. Sodani P. Zei T. Jacucci R. °Aristei C. °Latini P. °Raimondi C and Martelli MF. Section of Hematology and BMT Unit. °Radiotherapy Oncology, University of Perugia. 06122 Perugia, Italy.

T cell-depletion of the donor bone marrow prevents GvHD in matched BMT recipients, but this benefit is offset by an increased risk of graft failure and leukemia relapse. One approach to improving disease-free survival of TCD transplants recipients, is to employ intensified conditioning regimens. More intensive pre-transplant immunosuppression and myeloablation should compensate for the loss of the anti-host and anti-leukemic effects mediated by donor T cells and thereby overcome resistance to engraftment and provide a greater anti-leukemic activity. To this end, we designed, in 1989, a new conditioning regimen that added ATG and thiotepa (TT) to Cy and 1440 cGy hyperfractionated TBI, to enhance both immunosuppression and myeloablation. From June 1989, 54 patients (33 M, 21 F; median age 29 years, range 6-53) with acute leukemia (30 AML, 24 ALL) in hematological remission (22 CR I, 14 CR II) or relapse (N=18) received HLA-identical BMT depleted of T cells by the soybean agglutinin and E-rosetting technique. No additional post-transplant immunosuppressive treatment was given. All patients engrafted with a full-donor type chimerism. Neither acute nor chronic GvHD occurred in any evaluable patient. Of the 36 patients in remission at transplant, 24 survive event-free at a median follow-up of 50 months (range 26-78) with a PS 100%, 6 relapsed (2AML, 4 ALL) and 6 died from TRM. Of the 18 in relapse at transplant, 4 survive event-free at a median follow-up of 44 months (range 30-46), 7 relapsed (2AML,5ALL) and 6 died from TRM. We believe that TT enhances the cytoreductive effect of the conventional conditioning regimens in T-depleted BMTs and that there is a GvL effect mediated by the expansion of immunocompetent lymphocytes in the absence of GvHD when no cyclosporine is given.

60 P

PRECLINICAL PHARMACOLOGY AND DRUG SYNERGISM STUDIES OF PEG-ASPARAGINASE (PEG-ASNase) AND CYTARABINE (ara-C) IN LEUKEMIA CELL LINES.

AP Periclou, VI Avramis
Department of Pediatrics, USC, School of Medicine, Childrens Hospital LA, Los Angeles, CA 90027.

We have performed combination studies with these drugs in the leukemia cell lines, CEM/0 and CEM/ara-C/7A, a 50% resistant to ara-C line. The IC_{50} values of ara-C were 0.032 μM and 0.11 μM in these lines, respectively. The IC_{50} values of PEG-ASNase alone were 0.002 IU/ml and 1.52 IU/ml, respectively. The CEM/ara-C-7A is also 681-fold cross-resistant to PEG-ASNase as compared to CEM/0. The concurrent drug administration for 48 hours resulted in IC_{50} values of 0.56 nM for ara-C and 0.56 mIU/ml for PEG-ASNase in CEM/0 or a 57.4-fold synergism compared to ara-C alone, as estimated by the Median Effect Principle theory. In the CEM/ara-C-7A cell line, the co-incubation for 48 hours resulted in IC_{50} values of 15 nM for ara-C and 15 mIU/ml for PEG-ASNase or a 7.25-fold synergism as compared to ara-C and 101.1-fold synergism in comparison with PEG-ASNase alone. The combination of ara-C and PEG-ASNase in this cell line produced significant collateral sensitivity to PEG-ASNase. We determined that these drugs are highly synergistic against leukemia cell lines sensitive or partially resistant to ara-C. Hence, we conclude that the use of PEG-ASNase in combination with nucleoside anabolites may benefit leukemia patients with early relapse.

61 P

COMPREHENSIVE GERIATRIC ASSESSMENT: A NEW APPROACH TO ASSESS THE GLOBAL HEALTH STATUS OF ELDERLY PATIENTS WITH CANCER TO BE ENTERED IN CLINICAL TRIALS.

R.Bordonaro, L. Fratino, S.Monfardini. Division of Medical Oncology, Centro di Riferimento Oncologico- Istituto Nazionale Tumori Centroeuropeo. Aviano - Italy.

Aging is one of the most important risk factor for cancer. Despite in western countries nearly 60% of all tumours occurs in individuals aged 65 years or more, data from clinical research on elderly are scanty because older patients tend to be excluded from cancer clinical trials. This trend is particularly evident in lymphoproliferative diseases; for this reason the treatment of leukemia and lymphoma in the elderly has not achieved the same results as in younger patients. In addition to cancer, elderly are very often affected by concomitant chronic diseases, functional limitations and they are more vulnerable to iatrogenesis. They also are often socially isolated and economically deprived. Many Authors have stressed the limits of P.S. evaluation and the need of a practical tool to completely evaluate health status of elderly cancer patients. With the aim to provide a baseline picture of the main parameters that may contribute to identify subsets of elderly patients for clinical trial entry we created a Multidimensional Assesment Protocol for Cancer in Elderly (MACE) that collected information on socio-economic status, depression, physical performance and disability. Information on psycho-physical health condition is collected by Mini-Mental State Evaluation, Geriatric Depression Scale, Physical Performance Test, while social context and functional status is collected by Activity of Daily Living and Instrumental Activity of Daily Living questionnaire. The validation was performed by testing the MACE compared to the Sickness Impact Profile on thirty consecutive elderly patients with solid or hematological tumours, three times a week by two different physicians. The analysis indicates that this structured evaluation of functional status is feasible and reliable.