

Biological response modifiers

577

AMIFOSTINE REDUCES CUMULATIVE CISPLATIN NEPHROTOXICITY

R.L. Capizzi, B.S. Scheffler, W. Oster, N. Habboubi, P.S. Schein
U.S. Bioscience, West Conshohocken, PA, U.S.A.

Cisplatin nephrotoxicity is cumulative and generally persists after cisplatin is discontinued. Following appropriate hydration, 740–910 mg/m² Ami and 120 mg/m² cisplatin were administered to 74 patients every 28 days. Objective responses were noted in 46, 53 and 83% of patients with melanoma, head and neck and non-small cell lung cancers, respectively. $\geq 40\%$ decrease in creatinine clearance following ≥ 4 cycles of 120 mg/m² cisplatin occurred in only 6% (3/49) of patients. These results are consistent with nephroprotective effects in the Ami arm of the randomized trial of cisplatin (P) (100 mg/m²) and cyclophosphamide (C) (1000 mg/m²) $\pm$ Ami (910 mg/m²) in patients with advanced ovarian cancer in which only 10% (9/88) of the Ami-treated patients vs 32% (29/91) of control patients ($P < 0.001$) had $\geq 40\%$ reduction in creatinine clearance after ≥ 4 cycles of CP therapy. The 32% incidence of cisplatin-induced reduction in creatinine clearance observed in the control patients of this randomized trial is comparable to literature reports of 35–45% incidence of $\geq 40\%$ decrease in creatinine clearance following cumulative cisplatin doses of 400–600 mg/m². Thus, Ami's reduction of cumulative renal toxicity to 6–10% following repetitive doses of 100–120 mg/m² cisplatin represents a significant adjunct to preserve renal function. The high response rates reflect selective cytoprotection for normal tissues.

ORAL

578

G-CSF (FILGRASTIM) FOR MOBILIZATION OF STEM CELLS IN HEALTHY DONORS

S. Singhal, R. Powles, S. Cabral, J. Treleaven, J. Mehta
Royal Marsden Hospital, Surrey, U.K.

Ten healthy donors (5 M, 5 F; 15–50 years, median 35.5) who had previously donated BM for related patients (6 HLA-mismatched, 4 HLA-matched) underwent leukapheresis on 1–4 consecutive days (median 2) on a Cobe Spectra cell separator. Stem cells mobilized with 4–13 $\mu\text{g/kg}$ G-CSF (Neupogen, Amgen) for 4–6 days. The cells were harvested for treatment of graft failure ($n = 5$) or for adoptive immunotherapy of post-transplant relapse ($n = 5$). The leukocyte count increased from $4.9\text{--}12.6 \times 10^9/\text{L}$ (median 7) before G-CSF to $22.4\text{--}55.1 \times 10^9/\text{L}$ (median 31.5) on the first day of the harvest ($P = .004$). The yields were $0.46\text{--}11.6 \times 10^8$ mononuclear cells/kg patient body weight (median 7.3). A total of 26 apheresis procedures were performed, and the yield per procedure was $0.46\text{--}4.5 \times 10^8$ MNC/kg (median 2.8). It was possible to obtain adequate dual peripheral venous access in all donors. No donor experienced procedure-related complications on the cell separator. Seven donors reported bodyache which responded well to paracetamol, and fever or flu-like symptoms were not reported. We conclude that (1) G-CSF administration is tolerated well by normal donors, (2) this results in marked leukocytosis which is not associated with any adverse events, and (3) it is possible to mobilize adequate progenitor cells from normal donors for primary transplantation into patients.

ORAL

579

SELECTIVE CARDIOPROTECTION OF RAT HEART MYOCYTES EXPOSED TO DNA INTERCALATING AGENTS USING AMIFOSTINE (AMI) AND ITS DEPHOSPHORYLATED METABOLITE, WR-1065

R.T. Dorr, S. McLean, D.S. Alberts, L. Speicher, R.L. Capizzi
Arizona Cancer Center, Univ of Arizona, Tucson, AZ and US Bioscience, West Conshohocken, PA, U.S.A.

The DNA intercalators, doxorubicin, daunorubicin and mitoxantrone, produce cumulative-dose-limiting cardiomyopathy. Using a rat heart myocyte model (Ca Res 48:5222, 1988), the cardioprotective effect of Ami and WR-1065 were evaluated in beating heart cells exposed for 1 hr to inhibitory concentrations of each intercalator. Viability was determined by the degree of ATP depression, normalized to cellular protein. Both Ami and WR-1065 resulted in significant protection of heart cells. 15 min pretreatment with Ami or concurrent exposure to either Ami or WR-1065 with the intercalators protected heart cells from ATP loss

ORAL

and cessation of beating. Post-treatment with either thiol was ineffective. The maximal concentration of either thiol used was 2.0 $\mu\text{g/mL}$ which is 1/20 the clinically-achievable plasma concentration of Ami in humans following 910 mg/m². These thiol exposures slightly increased cellular glutathione levels. A similar 15 min pretreatment of the human ovarian cancer 2780 tumor cell line with Ami did not protect from drug-induced cytotoxicity with numerous agents including doxorubicin, cisplatin, mitomycin and paclitaxel. These findings demonstrate that selective cardioprotection with Ami is achievable with clinically attainable concentrations.

580

ASSESSMENT OF INTERLEUKIN-2-INDUCED CARDIOVASCULAR TOXICITY BY CARDIAC ECHOCARDIOGRAPHY

G. Di Lucca, G. Citterio, G. Fragasso, E. Rossetti, U. Scaglietti, M. Tresoldi, C. Rugarli, S.E. Chierchia
IRCCS H S. Raffaele, Milan, Italy

Cardiovascular toxicity related to i.v. administration of Interleukin-2 (IL-2) is the main cause of treatment withdrawal and it is unpredictable on the base of standard pre-treatment evaluations including history, physical examination and EKG. We performed this study to investigate the value of Cardiac Ultra Sono Scan (CUSS) in the detection and prediction of such toxicity. The study included 19 patients (15 males, 4 females, median age: 51, tumor type: 10 advanced renal cell cancer, 9 malignant melanoma) scheduled to receive multiple cycles of IL-2 by continuous i.v. infusion at the dose of 18 MIU/m²/day for 96 hours. Data were recorded from 31 IL-2 infusions: a marked impairment of diastolic function was observed in all cases, but in a subset of cycles (12/31) this function was already impaired at the pre-treatment determination, and this was significantly correlated with the onset of major cardiovascular side-effects conditioning treatment discontinuation ($P < 0.05$). Among the parameters studied, the ratio of maximal flow velocity in early diastole to that obtained in late diastole (E/A), as measured by transmitral flow pattern analysis, resulted not only the most sensible index of impairment of the diastolic function induced by IL-2, but also an accurate predictor of cardiovascular toxicity when altered before treatment. An abnormal E/A was significantly correlated with a history of hypertension ($P < 0.05$). We conclude that CUSS is an effective procedure and may contribute to identify patients with increased risk for cardiovascular toxicity due to IL-2.

ORAL

581

IMMUNOTHERAPY IN CERVICAL CANCER PATIENTS

A.N. Flander, M. Nimako, M. Adams, A.S. Evans, S. Mann, D. Westmoreland, S. Stacey, J. Hickling, S. Inglis, L.K. Borysiewicz
University Hospital of Wales and Velindre Hospital, Cardiff, U.K.

A phase 1 study aiming to generate MHC class 1 restricted HPV specific cytotoxic lymphocytes (CTL's) in cervical cancer patients using vaccinia recombinant (TA-HPV) immunotherapy encoding E6 and E7 open reading frames of HPV 16 and 18. In addition the trial monitors toxicity and environmental contamination.

ORAL

The construct has been used to vaccinate 8 patients to date with established cervical carcinoma by conventional scarification under strict isolation to avoid environmental release. Assays have been developed to detect HPV E6 and E7 specific CTL using adenovirus recombinants for secondary *in vitro* stimulation to avoid non-specific cytotoxicity.

Clinical follow-up is still in progress but no side-effects of vaccination have been observed up to a year post vaccination, despite subsequent radio- and chemotherapy. No environmental contamination has been detected and the recombinant has been shown to be stable after human inoculation. Serological response to the inserted sequences has been observed in some of the patients and cytotoxicity assays suggest the development of HPV specific CTL.

Adjuvant immunotherapy for women with cervical carcinomas using a vaccinia recombinant agent encoding HPV 16/18 E6 & E7 appears promising. Further work is planned to define dosage scheduling and the ideal recipient group.