demonstrate that mutant MGMT after an IRES facilitates the selection of cells expressing a gene that is therapeutic for a human disease. This model should be useful for gene therapy of human LAD, and may be a prototype for gene therapy for other single gene defects.

SOLID TUMORS

51

EUROPEAN EXPERIENCE OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR METASTATIC RENAL CARCINOMA: ON BEHALF OF THE FRENCH ITAC GROUP AND THE EBMT SOLID TUMOUR WORKING PARTY

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The immunological graft-versus-tumor (GVT) effect has been reported in various solid cancers after allogeneic hematopoietic stem cell transplantation (HSCT). We evaluated the experience of allogeneic HSCT for renal cell carcinoma (RCC) in Europe. **Methods and Patients:** We report the data on 124 patients with clear cell RCC, median age 52 years (range 18-68) transplanted in 21 European centers. Various reduced intensity conditionings (RIC) based on fludarabine were used. All patients received allogeneic peripheral blood cells: 106 from an HLA-identical sibling, 5 from mismatched related donor and 13 from matched unrelated donor (MUD). GVHD prophylaxis consisted of cyclosporine A (CyA) alone, or combined with methotrexate or mycophenolate mofetil. All patients with mismatch or MUD received anti-T-lymphocyte immunoglobulin. Donor lymphocyte infusions (DLI) were given to 42 patients. The median follow-up was 15 months (range 3-41). **Results:** All but 3 patients engrafted. The cumulative incidence of grades II-IV acute graft-versus-host disease (GVHD) was 40% and for chronic GVHD it was 33%. Transplant-related mortality was 16% at one year. Complete (n = 4) or partial (n = 24) responses, median 150 (range 42-600) days posttransplant, were associated with time from diagnosis to HSCT, mismatched donor and acute GVHD II-IV. Factors associated with survival included chronic GVHD (hazards ratio, HR 4.12, $P < .001$), DLI (HR 3.39, $P < .001$), <3 metastatic sites (HR 2.61, $P = .002$) and a Karnofsky score >70 (HR 2.33, $P = .03$). Patients with chronic GVHD and given DLI (n = 17) had a 2-year survival of 70%. **Conclusions:** Our data demonstrate that i) RCC patients with less than 3 metastatic locations and a Karnofsky score >70% may be considered for HSCT, ii) RIC and allogeneic HSCT is feasible in RCC patients with a low non-progression-mortality (16%), iii) a clinically meaningful GVT effect can be generated in these patients, often associated to DLI and chronic GVHD.

STEM CELL BIOLOGY

52

GENE EXPRESSION ANALYSIS OF CIRCULATING HEMATOPOIETIC PROGENITOR CELLS FROM IRRADIATED MICE AND HUMANS PROVIDES A MOLECULAR PROFILE OF RADIATION INJURY

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The risk for terrorist-mediated nuclear or radiological attack has been identified as a major threat to the United States in the coming decade. Radiation exposure can cause a spectrum of hematological toxicities, from mild immunosuppression to myeloablation with concordant life threatening complications. Accurate biological dosimetry will be critical, therefore, for caregivers to triage individuals to the appropriate medical management. Currently, biodosimetric tools include lymphocyte depletion kinetic and cytogenetic analysis, both of which require several days for results to be obtained. We propose that high throughput genomic analysis of peripheral blood mononuclear cells (PB MNCs) can sensitively identify patterns of molecular changes which occur following different levels of radiation exposure. In this study, we collected primary PB MNCs from 10 week old C57Bl6 mice at 6 hours following 4 different levels of radiation exposure: normal (non-irradiated), 50 cGy (trivial exposure), 200 cGy (myelosuppressive) and 1000 cGy (lethal). RNA was extracted and used for synthesis of probes for hybridization to spotted arrays. We performed a binary regression analysis to elucidate patterns of gene expression to distinguish between a normal animal and one that had been exposed to various levels of radiation. Distinct gene expression patterns were evident within PB MNCs at each of the 4 exposure levels, demonstrating the feasibility of this approach. We found that the selected metagene pattern for "normal" was able to distinguish normal from 50 cGy, 200 cGy and 1000 cGy exposure with 100% predictive capacity. The predictors selected for 50 cGy, 200 cGy and 1000 cGy were equally powerful at distinguishing these levels of exposure from all others. These data demonstrate the power of this approach to correctly distinguish clinically relevant levels of radiation exposure. In order to validate these molecular predictors generated in mice as profiles of human radiation response, we are currently testing, in a blinded manner, whether these predictors can distinguish different levels of radiation exposure in human PB samples collected from patients who have undergone 200 cGy or 1000 cGy total body irradiation. These validated biomarkers of radiation response can serve as templates for rapid screening tests for radiation exposure and, more broadly, are potential targets for therapeutic intervention.

SUPPORTIVE CARE

53

A PHASE II, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF THE SAFETY AND EFFICACY OF VELAFERMIN (CG53135-05) ADMINISTERED INTRAVENOUSLY AS A SINGLE DOSE FOR THE PREVENTION OF ORAL MUCOSITIS IN PATIENTS RECEIVING AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANT (AHSCT)

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Velafermin (CG53135-05 or recombinant human fibroblast growth factor-20) is under investigation for the prevention of oral mucositis (OM). OM is a common side effect in patients (pts) receiving high-dose chemotherapy (HDCT) with or without total body irradiation (TBI) as conditioning regimen for AHSCT. Preclinical studies have demonstrated that velafermin promotes epithelial and mesenchymal cell proliferation in vitro and that a single dose of velafermin had activities in reducing the severity and duration of OM as effective as multiple doses. Previous clinical data suggested that velafermin could be safely given at doses up to 0.2 mg/kg. The objectives of this phase II trial were to evaluate the safety and efficacy of velafermin in preventing severe OM from approximately 200 pts undergoing HDCT with or without TBI for an AHSCT in the US. Patients were equally randomized to one of four arms: placebo, or velafermin 0.03, 0.1 or 0.2 mg/kg. Pts received a single intravenous dose of velafermin or placebo 24-36 hrs after completion of the stem cell infusion and were monitored daily until they were discharged from the hospital or until neutrophil engraftment established (defined as first day of absolute neutrophil counts $\geq 500/\mu$ in this study). The primary end point was the incidence of OM (World Health Organization (WHO) score of grade 3 or 4). Secondary end points included duration of severe OM, area under the curve of all OM, days with alternative nutrition, and narcotic analgesic use. Patient enrollment was completed with 212 pts randomized. Approximately 2/3 were multiple myeloma pts receiving high dose melphalan as conditioning regimen and 1/3 of them were lymphoma pts. Less than 10% of pts had TBI as part of their conditioning regimen. Preliminary blinded aggregate data from 160 pts indicated that study drug was generally well tolerated. 30% of pts did not develop any OM and 32% pts developed grade 3/4 OM with a duration of 4.8 ± 3.7 (mean ± sd) days among the pts with severe OM. Most adverse events (AE) were mild to moderate in severity with most frequent serious AEs being neutropenic fever, pneumonia and pyrexia. The trial was monitored by a Data Safety Monitoring Board (DSMB). The results of the primary end point of grade 3/4 OM from each treatment arm or placebo as well as 30-day safety information from all pts will be reported.

54

INVASIVE ASPERGILLOSIS FOLLOWING HSCT: OUTCOMES AND PROGNOSTIC FACTORS ASSOCIATED WITH MORTALITY

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Invasive aspergillosis (IA) is a common cause of infection-related mortality in hematopoietic stem cell transplant (HSCT) recipients, despite appropriate therapy. Factors influencing outcomes have not been fully elucidated. To determine prognostic factors associated with mortality we retrospectively reviewed all cases of proven and probable IA diagnosed in HSCT recipients at the Fred Hutchinson Cancer Research Center (FHCRC) from 1st Jan 1990 to 31st Dec 2004. All-cause and attributable mortality were recorded. Prognostic factors identified in univariate analysis ($P < .10$) were further analyzed using a Cox multiple regression model. All variables except those occurring before HSCT were modeled as time dependent. 408 cases were identified: 238 proven and 170 probable IA. The probability of overall mortality at 1 year after diagnosis was 70% in patients diagnosed from 2002 to 2004 versus 86% among those diagnosed prior to 2002 ($P < .0001$). Cord blood as stem cell source (HR = 3.7 [1.0-13.2]), severe pulmonary function test abnormality pre-HSCT (2.3 [1.2-4.2]), increased creatinine (2.9 [1.9-4.3]) and bilirubin (6.2 [4.4-8.7]) at time of diagnosis of IA, monocytopenia (2.3 [1.6-3.2]), CMV disease (1.4 [1.0-1.8]), receipt of antithymocyte globulin (2.2 [1.5-3.3]), disseminated IA (2.0 [1.4-2.7]), and IA later after HSCT (>40 days) (2.8 [2.0-4.1]) were independently associated with increased all-cause mortality; receipt of non-myeloablative HSCT (0.5 [0.3-0.7]) was independently associated with decreased mortality. The probability of mortality attributable to IA at 1-year was 26% in patients diagnosed from 2002 to 2004 versus 49% among those diagnosed prior to 2002 ($P = .007$). Mismatched HSCT (2.1 [1.2-3.7]), increased creatinine (3.3 [1.8-6.1]) and bilirubin (5.5 [3.3-9.3]), receipt of antithymocyte globulin (2.3 [1.2-4.1]), disseminated IA (4.0 [2.5-6.3]) and IA later after HSCT (2.4 [1.2-4.0]) were independently associated with increased attributable mortality; non-myeloablative HSCT (0.3 [0.1-0.8]) and receipt of voriconazole therapy (0.4 [0.2-0.8]) were independently associated with decreased mortality. In this study we have demonstrated a significant decline in mortality in patients diagnosed with IA following HSCT in the time period 2002-2004, compared with prior to 2002. This finding has coincided with increased use of non-myeloablative conditioning regimens and voriconazole; two factors we have identified to be protective.