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Successful allogeneic bone marrow transplantation (BMT) following orthotopic liver transplantation (OLT) for fulminant hepatic failure and severe aplastic anemia (SAA) due to non A non B non C hepatitis.

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A PHASE I TRIAL OF HIGH-DOSE MELPHALAN, MITOXANTRONE AND CARBOPLATIN IN PATIENTS WITH OVARIAN AND BREAST CANCER. C.H. Weaver, F. Wittlin, M. Lewis, L.S. Schwartzberg, W. Li.* and P. Palmer.* Clinical Trials Division, Response Technologies Inc., Memphis, TN.

Melphalan, mitoxantrone and carboplatin are chemotherapeutic agents known to be active in the treatment of ovarian cancer. Melphalan and mitoxantrone have been demonstrated to have in vitro synergistic cytotoxicity against MCF-7 cell lines. Their maximal tolerated dose has previously been reported to be melphalan 180 mg/m^2 and mitoxantrone 60 mg/m^2. Carboplatin has equal efficacy to cisplatin in the treatment of ovarian cancer and is more suitable for dose escalation. A high-dose chemotherapy regimen utilizing melphalan, mitoxantrone and carboplatin may be active in the treatment of patients with ovarian or breast cancer. We performed a dose escalation trial to determine the maximal tolerated dose of carboplatin that could be administered with a fixed dose of melphalan 160 mg/m^2/IV on day 1 and mitoxantrone 25 mg/m^2/IV/day on days 1 and 2. Sequential cohorts of patients received carboplatin 1000-1600 mg/m^2/IV over 60 minutes on day 2 with PBPCs subsequently infused on day 5. All drugs were administered IV over 45-60 minutes and all patients received rhG-CSF 6μg/kg/sc/day until neutrophil recovery. A total of 30 consecutive patients with ovarian (n=22) or breast (n=8) carcinoma were enrolled. No unresolved grade 3 or 4 non-hematologic toxicity was observed at carboplatin doses of 1000 mg/m^2, 1200 mg/m^2 or 1400 mg/m^2 in successive cohorts of 4 patients. The initial 2 patients receiving carboplatin 1600 mg/m^2 experienced unresolved grade 4 toxicity. One patient developed sepsis and renal failure leading to death and the second developed grade 4 stomatitis leading to esophageal necrosis. A total of 20 patients were enrolled at the 1400 mg/m^2 cohort and 16 are currently evaluable. Grade 3-4 mucositis was observed in 68.7% of patients and 1 patient died from an intracerebral hemorrhage with a platelet count of 25.0 x 10^9/L on day +11 for a

		Grade 3-4 Toxicity		
Carboplatin	n	Liver	Mucositis	N&V
1400 mg/m^2	16	2/16	1/16	12/16
1600 mg/m^2	2	1/2	2/2	2/2

100 day TRM rate of 6.2%. The median AUC for carboplatin was determined to be 21.6 (range 7.2-39.8). Regression analysis was performed and no relationship was determined between the AUC and grade 3-4 non-hematologic toxicity or engraftment kinetics. Phase II trials in ovarian cancer are ongoing to evaluate the activity of this high-dose chemotherapy regimen.

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A RANDOMIZED PHASE IIB TRIAL COMPARING HIGH-DOSE BUSULFAN, MELPHALAN AND THIOTEPA (BuMelT) WITH CARMUSTINE, ETOPOSIDE, CYTOSINE ARABINOSIDE AND CYCLOPHOSPHAMIDE (BEAC) FOLLOWED BY PERIPHERAL BLOOD PROGENITOR CELL (PBPC) INFUSION IN PATIENTS WITH RELAPSED LYMPHOID MALIGNANCIES. C.H. Weaver, K. Tauer, M. O'Rourke, S. Rhinehart, K. Pendergrass, L.S. Schwartzberg, and Wei Li.* Clinical Trials Division, Response Technologies, Inc., Memphis, TN.

High-Dose BEAC followed by autologous stem cell transplant has recently been demonstrated to be superior to salvage therapy with DHAP for the treatment of patients with relapsed non-Hodgkin's lymphoma. Several high-dose chemotherapy preparative regimens have been reported for the treatment of lymphoid malignancies, but few have been evaluated in randomized clinical trials. Between 11/1/93 and 12/12/94, we randomized 50 consecutive patients with relapsed lymphoid malignancies and adequate PBPCs previously collected to receive high-dose BEAC or BuMelT followed by PBPC infusion. All patients received rhG-CSF 6 μg/kg/sc/day until neutrophil recovery. The 2 arms of this study were comparable with regard to histologic grade, initial stage, presence of B symptoms, age, gender, phase of treatment, prior radiotherapy and chemotherapy response, and number of infused CD34$^+$ cells. All patients were prospectively evaluated for toxicity according to the NCI common toxicity criteria and are a minimum of 100 days from PBPC infusion. Grade 3/4 diarrhea occurred in 7 versus 0 (p=0.01), mucositis in 18 versus 3 (p<0.001) and nausea in 15 versus 5 (p=0.04) patients receiving BuMelT and BEAC, respectively. Treatment related mortality was observed in 1 patient each receiving BuMelT and BEAC at 96 and 98 days following PBPC infusion, respectively. The patient receiving BuMelT succumbed to Pneumocystis carinii pneumonia and the patient receiving BEAC died from Idiopathic Pneumonia Syndrome with biopsy evidence of diffuse alveolar damage. A median of 9 days was required to achieve an ANC ≥ 500 in both treatment groups (p=0.37). A median of 9 (4-32) and 10 (7-45) days were required to achieve platelet transfusion independence in patients receiving BEAC and BuMelT respectively (p=0.17). Patients receiving BuMelT and BEAC required a median of 13 (range 9-40) and 11 (7-21) inpatient hospital days, respectively (p=0.03). Patients receiving BuMelT have significantly more gastrointestinal toxicity than patients receiving BEAC. A randomized phase III trial is currently ongoing to evaluate the efficacy of these 2 regimens across histologic subgroups in patients with lymphoid malignancies.

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PHASE I TRIAL OF SEQUENTIAL HIGH DOSE CHEMOTHERAPY WITH GCSF PRIMED PERIPHERAL BLOOD STEM CELL RESCUE IN PATIENTS WITH ADVANCED CANCER. D. Weckstein, K. Sprague*, C. Hurley*, D. Karp*, E. Berkman, P. Curtin, D. Schenkein, M. Sweet*, K. Miller. New England Medical Center, Boston, MA 02111

The use of GCSF primed peripheral blood stem cells (PBSC) as a source of hematopoietic reconstitution allows for rapid recovery from neutropenia and thrombocytopenia after high dose chemotherapy. 16 patients with advanced malignancy (small cell lung, ovarian, lymphoma, breast, sarcoma, cervical, medulloblastoma) have been treated on the following schedule: Cycle I cyclophosphamide 4 gm/m2 followed by GCSF 10 mcg/kg per day from day +2 until large volume leukophoresis (LVL) when WBC is >1,500. Cycles II through 5 CCE cyclophosphamide 3 gm/m2, carboplatinum 1gm/m2, and etoposide 180-540 mg/m2 (dose escalation) followed by infusion of 1/4 of the PBSC collection on the 3rd day after completion of chemotherapy. GCSF 5 mcg/kg per day is administered until ANC >1,000 x2 days. All treatment is delivered in an outpatient setting. LVL is performed over 1-4 days (median 2) with CD34 collection ranging from 4.7 x 10^6 per kilogram to 5.7 x 10^7 per patient. Therefore patients receive a minimum of 1 x 10^6 per kg CD34 cells after each cycle of CCE. 54 cycles of high dose therapy have been administered to 16 patients. 28 cycles have been complicated by hospitalization (22 cycles for fever and neutropenia). The median duration of hospitalization is 4 days. 38 cycles of combination CCE have been administered. The median number of days to ANC >500 is 11 days. The median time to platelet >20k without transfusion is 12 days. The median interval between treatment cycles is 21 days. Toxicity: no deaths attributable to therapy have occurred in 16 patients. 2 patients have been withdrawn from study for prolonged thrombocytopenia (transfusion dependent for 5 weeks after PBSC infusion). One cycle of therapy was complicated by Grade IV infection and one cycle complicated by grade IV diarrhea. There was no other Grade IV non hematologic toxicity. Of 11 patients who are accessible for tumor response, there have been 2 CR's (ovarian, breast) and 5 PR's (ovarian 1, germ cell 1, sarcoma 1, small lung 2). Extremely dose intense chemotherapy can be administered on an outpatient basis with acceptable toxicity with the use of cyclophosphamide/GCSF mobilized PBSC support.

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SUCCESSFUL ALLOGENEIC BONE MARROW TRANSPLANTATION (BMT) FOLLOWING ORTHOTOPIC LIVER TRANSPLANTATION (OLT) FOR FULMINANT HEPATIC FAILURE AND SEVERE APLASTIC ANEMIA (SAA) DUE TO NON A NON B NON C HEPATITIS. D.J. White,* T.J. Nevill, and V.C. McAlister. * Division of Hematology/Medical Oncology and Department of Surgery, Dalhousie University, Victoria General Hospital, Halifax, NS.

A 15-year-old male presented in July 1994 with nausea, vomiting, abdominal pain, and fulminant hepatic failure. Hepatitis A, B, and C serologies were negative. A cadaveric female donor liver became available, and on August 4, 1994, OLT was carried out uneventfully. Preoperative hemoglobin (Hb) and WBC were normal with a platelet count of 106 x 10^9/L. Post-operative Hb and WBC were initially normal, however bone marrow examination was carried out to evaluate progressive thrombocytopenia (29 x 10^9/L on August 16, 1994) which suggested decreased megakaryocyte numbers. Over the next two weeks, the patient became neutropenic and both platelet and red cell transfusion dependent. Repeat bone marrow exam on August 25, 1994, confirmed severe aplastic anemia with subsequent cytogenetic analysis showing a normal male karyotype. An HLA-identical sister was identified, and following cyclophosphamide (200 mg/kg) and ATGAM (90 mg/kg) conditioning, the patient received an allogeneic BMT on September 29, 1994. Pre-conditioning liver function was normal aside from ALT 64 (N ≤ 41) and GGT 81 (N ≤ 40). Graft-versus-host disease (GVHD) prophylaxis was with FK-506, methotrexate, and corticosteroids. Initial post-transplant course was unremarkable; liver function remained stable, and GVHD did not develop. WBC and platelet engraftment were prompt, but the patient required red cell support for approximately 100 days post-BMT due to ABO-incompatibility (marrow donor A positive, liver donor and recipient both O positive). The patient remains on FK-506 and Prednisone but continues to do well thirteen months post-OLT and eleven months post-BMT, with normal hepatic function and no clinical evidence of chronic GVHD. Allogeneic BMT can be successfully performed in patients following OLT and should be considered the treatment of choice in these patients if they develop SAA.