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PRELIMINARY RESULTS OF PHASE II TRIAL OF CLOFARABINE WITH PARENTERAL BUSULFAN FOLLOWED BY ALLOGENEIC RELATED OR UNRELATED DONOR TRANSPLANTATION FOR THE TREATMENT OF HEMATOLOGIC MALIGNANCIES AND DISEASES

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Background: Nonablative transplant regimens are useful to treat patients who are elderly or too ill to undergo a full-intensity ablative allogeneic transplant regimen. However, this approach is limited by a higher relapse rate in some situations. We developed a novel conditioning regimen using the nucleoside analogue clofarabine (CLO) with busulfan (BU) to treat elderly patients with acute leukemia or high risk MDS who are not in remission or are at high risk of relapse. **Methods:** Seven patients were enrolled on this single institution; phase II, IRB-approved trial, so far. The diagnoses at the time of transplant were four with AML, one with ALL, and two with MDS. At the time of study entry, six patients had persistent/relapsed disease and one was in remission. All patients received CLO 40 mg/m^2/day iv on d-8 through d-4 followed by BU 3.2 mg/m^2/day iv on d-3 and -2, followed by infusion of HLA matched related or unrelated donor PBSC on day 0. GVHD prophylaxis consisted of oral FK506 and MTX 5 mg/m^2 iv d + 1, +3 and +6. BU and CLO pharmacokinetic samples were collected on all patients for later PK analysis. **Results:** Primary endpoints included toxicity and response to therapy. There were no cases of hepatic, cardiac, or renal toxicity attributed to the conditioning regimen by d + 30. Acute toxicities included hand/foot syndrome, n = 2 (one grade 1, and one grade 3 by CTCAE v 3.0); fluid retention, n = 3 (2 grade 1 and 1 grade 2); nausea n = 5 (four grade 1 and 1 gr 2). One subject suffered respiratory failure of unknown etiology. That resolved completely and was deemed to be possibly related to the treatment. All patients had hematologic nadirs lasting 12 to 15 days. GCSF was used in 6 of 7 subjects. 7 of 7 patients achieved allogeneic engraftment with myeloid cells by day +30. Response to therapy was documented in 5 patients by d + 30, two are not yet evaluated. One (1) patient relapsed by d + 62, one relapsed by day +54. 3 of 5 remain in remission with follow up ranging from 91 to 152 days. **Conclusions:** CLO + BU is a novel allogeneic conditioning regimen that seems to be well tolerated by the small number of subjects treated so far at our institution. The follow up is not long enough to conclude more at this time. The study continues to accrue patients and will be updated at the meeting.

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NON-MYELOABLATIVE TRANSPLANTATION IS A FEASIBLE OPTION IN PATIENTS WITH ADVANCED HEMATOLOGICAL MALIGNANCIES: A SINGLE CENTER EXPERIENCE

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Introduction: There are limited therapeutic options in patients with advanced hematologic diseases. Historically patients with relapsed/refractory disease do not fare well after non-myeloablative allogeneic stem cell transplantation (NST). **Methods:** In an attempt to examine whether NST provides disease control in patients with high risk hematologic malignancies, we retrospectively evaluated our experience and analyzed the outcomes of NST in patients with high risk hematologic malignancies from 1999 to 2006. **Results:** Ten males and 4 females (n = 14) of median age 48 years (range: 19–65 years) were treated. Of these, only 4 patients were in complete remission (CR) at the time of transplantation and 10 patients were transplanted with active disease. All patients (n = 4) in CR at the time of transplantation had received one or two prior myeloablative stem cell transplantation. The majority of patients received peripheral blood stem cells (n = 12). One patient received bone marrow and one patient received cord blood derived stem cells. All patients engrafted. Median time for neutrophil recovery was 18 days (range: 10–29 days) and 22 days (range: 14–47 days) for platelets. In two patients, the platelet count did not drop below 20×10^3/μl and two patients died prior to platelet engraftment. Median duration of follow-up for those who did not succumb to early transplant-related mortality (<100 days) was 5.2 months (range: 105 days-2 years). Median survival time of this cohort was 125 days. Of the 14 patients, 9 have died. Four patients (30%) died within 100-days of transplantation. Overall survival (OS) of all patients who did not succumb to TRM was 44% at 14 months. No relapse occurred after 6 months. All 5 patients that are alive have chronic graft versus host disease. OS in patients transplanted in CR (n = 4) at 1-year was 50%, and was 44% for those transplanted with active disease (n = 10). Disease status at transplantation was not a significant variable for survival (p = 0.88). Most frequent cause of death was relapse/progression of disease (n = 5; 55%). **Conclusion:** In conclusion, NST provides a possible therapeutic option in a proportion of patients with high risk hematologic malignancies. Disease relapse prior to development of graft versus tumor effect remains the most frequent cause of failure in patients transplanted with active disease.

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RADIATION FOLLOWED BY MYLOTARG PLUS DLI FOR EXTRAMEDULLARY RELAPSE FROM ACUTE MYELOID LEUKEMIA POST-ALLOGENEIC TRANSPLANT

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Introduction: Extramedullary relapse of acute leukemia after hematopoietic cell transplant can occur in the form of granulocytic sarcomas and leukemia cutis. According to some published reports, they may occur in up to 20% of post-transplant patients. The treatment of these relapses has been center dependent, and no treatment protocol has been published which clearly shows superiority. We describe three patients with extramedullary relapse who were treated with a combination of radiation, gemtuzumab ozogamicin and DLI (donor leukocyte infusion). **Methods:** All three patients had a diagnosis of AML and had induction and consolidation therapy, followed by a myeloablative transplant with cytoxan and TBI as a preparative regimen. Two patients presented with chloromas and one presented with leukemia cutis as sites of recurrence. None had evidence of bone marrow recurrence, and relapse occurred from 4 – 11 months post transplant. All three were treated with focal radiation therapy to the site of relapse followed by gemtuzumab ozogamicin and DLI. The radiation doses were 20–30 Gy, followed by gemtuzumab ozogamicin 9 mg/m^2 given every two weeks for two doses. All three patients received DLI initially at $1.0 \times 10–7$ CD3+ cells/kg, and subsequently dose-escalated to $2.0 \times 10–7$. **Results:** All three patient achieved disease response. Median disease free survival has not been reached. One patient with leukemia cutis died of complication from acute GVHD 9 months after the first dose of DLI. The remaining two patients with chloromas are still alive and free of marrow relapse after two doses of DLI. **Conclusion:** The combination of focal radiation followed by gemtuzumab ozogamicin (9 mg/m^2) every two weeks for two doses, followed by dose escalating DLI is an option for patients with extramedullary relapse of acute leukemia following hematopoietic cell transplantation.

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RELATIVE CONTRIBUTION OF CD127 NEGATIVE SELECTION, RAPAMYCIN, AND TGF-β TO THE GENERATION OF HUMAN REGULATORY T CELLS THAT INHIBIT ALLOREACTIVITY VIA DENDRITIC CELL MODULATION

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Regulatory T cells (Tregs) express reduced IL-7Rα (CD127) and preferentially expand in rapamycin or TGF-β. Here, we evaluated the independent and combined effect of CD127 negative selection,