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MINIMAL RESIDUAL DISEASE PRIOR TO AUTOLOGOUS STEM CELL TRANSPLANTATION IN PATIENTS WITH ACUTE MYELOGENOUS LEUKEMIA AS A PREDICTOR OF RELAPSE

Rojas, A.M.[1], Song, S.X.[2], Corliss, A.[1], Truell, J.[2], Paquette, R.L.[1], Schiller, G.J.[1], Territo, M.C.[1] [1] UCLA Medical Center, Los Angeles, CA; [2] UCLA Medical Center, Los Angeles, CA.

The level of minimal residual disease (MRD) after consolidation has been reported in the past as being a strong predictor of relapse in patients treated with standard chemotherapy. We evaluated the presence of MRD in our adult patients with acute myelogenous leukemia (AML) after consolidation and just prior to autologous stem cell transplant. A total of 47 patients underwent autologous stem cell transplant for AML from June, 2002 through December, 2004. All patients were in first complete remission and had achieved this remission after induction chemotherapy using cytarabine and idarubicin, with the standard 7 + 3 regimen followed by one course of consolidation with mitoxantrone and high dose cytarabine. All patients had bone marrow obtained 2–4 weeks prior to transplant and were in complete remission as defined by morphology. Data were available on 42 of these patients to look for MRD by multiparametric flow cytomety at a sensitivity level of 0.5 to 1%. Out of these 42 patients, 15 (36%) had documented MRD detected on bone marrow biopsy prior to transplant. All 15 of the patients have relapsed and died. Of the 27 patients who did not have evidence of MRD going into transplant, 14 have relapsed. Thus despite lack of evidence of MRD, using our past techniques, relapse was seen in 52% of these patients. At this time we are in the process of evaluating a subsequent group of patients who underwent autologous stem cell transplant using a more sensitive assay for MRD. In conclusion, in spite of morphologic complete remission, evidence of MRD after consolidation and prior to autologous stem cell transplant was predictive of relapse. In the future, alternative treatment approaches should be considered for such patients.

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TREATMENT OF MYELOID MALIGNANCIES IN ELDERLY PATIENTS WITH FLUDARABINE AND TARGETED BUSULFAN (t-Bu) AND ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (HCT)

Fernandez, H.F., Henao-Uribe, A.M., Poling, W.H., Chavez, J.C., Alsina, M., Ayala, E., Field, T., Kharfan-Dabaja, M., Perez, L., Raychaudhuri, J., Ochoa-Bayona, L., Anasetti, C. H Lee Moffitt Cancer Center and Research Institute, Tampa, FL.

Despite the poor prognosis of elderly patients with standard chemotherapy, concerns with intensive conditioning regimens have limited the use of allogeneic HCT in this population. Reduced intensity regimes have emerged as an option for these patients. We treated twenty patients over the age of 60 with fludarabine and targeted busulfan (t-Bu). The median busulfan AUC received was 5244 mmol/min. Graft versus host disease (GVHD) prophylaxis consisted in tacrolimus and methotrexate (75%) and tacrolimus and mycophenolate mofetil (25%). Median age was 64.8 (60–69) years. Eleven were male (55%) and nine female (45%). Six patients (30%) had de novo AML, ten (50%) secondary AML and four (20%) high risk MDS. Five patients (25%) had high-risk disease in first complete remission (CR1) and five (25%) had AML in second complete remission (CR2). Ten patients were not in remission at the time of transplant. Donor sources included six (30%) HLA-matched siblings, 13 (65%) matched unrelated and one (5%) mismatched unrelated donor. A high Sorror Comorbidity Index (>3 points) was found in 35% of patients. Acute GVHD occurred in all the patients (65% Grade I/II, 35% grade III/IV). The median follow-up of survivors was 731 days (113–1149+). Non-relapse mortality was 10%. Relapse rate at 365 days was 45%. Disease-free (DFS) and overall survival (OS) at 365 days were 50.9 +/-12% and 61.30 +/-12% respectively.

Conclusion: Given the sub-optimal results of standard chemotherapy in this patient population and the low transplant related mortality and encouraging OS seen in our cohort, targeted RIC allogeneic HSCT should be considered as a feasible alternative in patients older than 60 years with high risk MDS/AML. Further study in this group is warranted.

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THERAPEUTIC CHOICES IN PATIENTS WITH PH1 (+) CHRONIC MYELOGENOUS LEUKEMIA LIVING IN DEVELOPING COUNTRIES IN THE TYROSINE KINASE INHIBITORS (TKI) ERA: STEM CELL TRANSPLANTATION OR TKI?

Ruiz-Arguelles, G.J.[1,2], Tarin-Arzaga, L.C.[3], Gonzalez-Carrillo, M.L.[2], Gutierrez-Riveroll, K.I.[1], Rangel-Malo, R.[2], Gutierrez-Aguirre, C.H.[3], Cantu-Rodriguez, O.G.[3], Gomez-Almaguer, D.[3], Giralt, S.[4] [1] Centro de Hematologia y Medicina Interna de Puebla, Puebla, Mexico; [2] Laboratorios Clinicos de Puebla, Puebla, Mexico; [3] Hospital Universitario, Monterrey, Nuevo Leon, Mexico; [4] MD Anderson Cancer Center, Houston, TX.

Seventy two patients with Ph1 (+) chronic myelogenous leukemia (CML) in a first chronic phase were followed during a 6-year period in two different institutions in México. Twenty two of them were given a reduced-intensity allogeneic stem cell transplantation, whereas 50 were treated with a tyrosine kinase inhibitor (TKI), mainly imatinib mesylate. The two groups were balanced in their salient features and the overall results of the treatment were statistically similar: The six-year overall survival (SV) for patients given an allograft was 77% and for patients given a TKI was 84% (p NS); whereas the median survival for both groups has not been reached, being above 71 and 90 months respectively (p NS). Most of the patients (91%) who were allografted elected this treatment because they were unable to afford the treatment with a TKI, whereas most of those treated with a TKI (84%) were given the treatment through institutions devoted to support the treatment of such individuals; only 16% were able to afford the treatment with TKI. The median cost of each allograft was 18 000 USD, an amount which is useful to afford 180 days of treatment with imatinib (400 mg/day) in México. Despite the fact that drug treatment is superior to allografting as first-line therapy in CML in chronic phase in developed countries, stem cell transplantation has still a relevant role in circumstances of limited resources. Cost considerations favor allogeneic stem cell transplantation as a one-in-a-life-time procedure in which lifelong drug treatment with an expensive drug represents an excessive burden on resources.

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RELAPSE OF ACUTE MYELOID LEUKMIA AFTER ALLOGENEIC STEM-CELL TRANSPLANTATION (SCT) WITH MYELOABLATIVE CONDITIONING IS ASSOCIATED WITH LONGER SURVIVAL THAN RELAPSE AFTER REDUCED-INTENSITY CONDITIONING (RIC)

Shimoni, A., Hardan, I., Shem-Tov, N., Rand, A., Ribakovsky, E., Yerushalmi, R., Nagler, A. Chaim Sheba Medical Center, Tel-Hashomer, Israel.

Relapse of AML/MDS after allogeneic SCT is associated with poor outcome. A subset of patients (pts) can be salvaged with DLI or with a second SCT. It was previously speculated that pts given RIC may have a better chance to be salvaged than pts failing high-dose conditioning. We retrospectively analyzed results of 171 SCTs for AML/MDS with iv busulfan (ivBu)-based regimens. 58 pts were eligible for myeloablative conditioning and were given standard ivBuCy. 57 were given RIC consisting of fludarabine (F) and ivBu (FB2, 6.4 mg/kg) and 56 were given a modified myeloablative conditioning consisting of F and full-dose ivBu (FB4, 12.8 mg/kg). Median age was 40 (17–64), 60 (43–75) and 52 (18–66) years, respectively ($p < 0.001$). 56% had active leukemia at SCT and 47% had unrelated donors with no difference between the regimens. With a median follow-up of 31 months (4–90), 70 pts relapsed, 20 after BuCy, 25 after FB2, and 25 after FB4, cumulative incidence 38%, 49% and 48%, respectively (p=NS). The median time to relapse was 5.3 (1–59), 3.4 (1–34) and 2.7 (1–30) months, respectively (p=NS); 65%,60% and 64% of all relapses occurred within 6 months of SCT, while 20%, 12% and 8% occurred after more than 2 years, respectively (p=NS). 25 pts were treated with immune-suppression withdrawal alone, 12 were given DLI with or without preceding low-dose chemotherapy, 33 were given intensive therapy either salvage chemotherapy followed by mobilized DLI (n = 24) or a second SCT (n = 9, 5 from a different donor). Treatment types were not significantly different among the

regimens. With a median follow-up of 15 months from relapse (0.5–52), 12 pts are alive, 9 in remission. The most important predicting factor for survival after relapse was the duration of remission. Pts relapsing > 6 months and < 6 months after SCT had a median survival of 7.2 and 1.4 months and estimated 2-year survival of 22% and 2%, respectively ($p < 0.001$). Survival rates were 20%, 0% and 4% after BuCy, FB2 and FB4, respectively ($p = 0.04$). SCT in refractory disease was also predictive of poor outcome after relapse ($p < 0.001$). Multivariable analysis determined short remission after SCT and conditioning with FB regimens as independent adverse factors with hazard ratios of 3.3 (1.9–6.3, $p < 0.001$) and 2.0 (1.0–4.0, $p = 0.04$), respectively. In conclusion the notion that pts given RIC can be salvaged more easily if they relapse is not substantiated and should not be a rationale to select RIC over myeloablative conditioning.

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FEASIBILITY OF CLOFARABINE CYTOREDUCTION BEFORE INITIATION OF ALLOGENEIC STEM CELL TRANSPLANT REGIMEN DURING THE CYTOPENIC PHASE FOR PATIENTS WITH REFRACTORY ACUTE MYELOGENOUS LEUKEMIA

Locke, F.L., Artz, A.S., Rich, E.S., van Besien, K., Stock, W. The University of Chicago, Chicago, IL.

Patients with refractory leukemia entering allogeneic stem cell transplant (Allo-SCT) fare poorly, and higher disease burden correlates with decreased disease free survival (DFS) (van Besien, JCO 2005). To determine the feasibility of clofarabine (CLO) cytoreductive therapy as a bridge to Allo-SCT we retrospectively analyzed 14 heavily pretreated refractory acute myelogenous leukemia (AML) pts. All pts received CLO 30–40 mg/m^2 intravenous daily for five consecutive days as bridging therapy with the intention to initiate Allo-SCT conditioning during the cytopenic phase, 14–21 days later. Pts had a mean of 2.2 prior treatment regimens, and 8 had primary refractory leukemia. 4 pts were relapsed following a prior stem cell transplant (1 autologous and 3 Allo-SCT).

To assess CLO cytoreduction, bone marrow (BM) biopsy and aspirate were performed at the nadir, day 12 after CLO. Cytoreduction was defined as post CLO marrow with <20% cellularity *and* <10% blasts. CLO achieved cytoreduction in 8/14 pts. The median BM cellularity was 45% (4–90%) before and 5% (1–83%) after CLO. The median BM blast % was 23% (10%-100%) before and 6% (0%-90%) after CLO.

Of the 14 pts, 13 proceeded to Allo-SCT by day 26 (median 22, range 17–26). 7 pts received a fludarabine, busulfan, campath regimen; 5 pts received fludarabine, melphalan with either ATG (2) or Campath (3); 1 pt received a TBI-based regimen. Grade 4 hyperbilirubinemia prevented one pt from proceeding to Allo-SCT preparative regimen.

Of the 13 pts receiving Allo-SCT the median follow up is 15 months for survivors. 3 pts are alive and disease free at 4.3, 16.5, and 40 months after Allo-SCT, and all achieved CLO cytoreduction. 2 pts are alive with progressive disease at 8 and 15 months. The overall DFS at day 100 was 9/13. 3 pts relapsed before day 100, 2 of whom did not achieve cytoreduction. Beyond day 100 an additional 3 pts relapsed at 5.5, 5.5, and 6.5 months. 1 pt died of treatment related motality (TRM), sepsis, at day 17. The TRM at day 100 was 1/13, and 4/13 at one year.

In conclusion, 13/14 patients with refractory AML were able to undergo Allo-SCT with acceptable TRM in this heavily pretreated group after CLO re-induction. Based on these data, we are pursuing a prospective feasibility study of CLO cytoreduction followed by Allo-SCT during the cytopenic phase.

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PLASMA AND CSF PHAMACOKINETICS (PK) AND RESPONSE TO DASATINIB IN A YOUNG CHILD WITH RELAPSING Ph+ ALL AFTER ALLOGENEIC TRANSPLANT

Morris, C.L.[1], Brown, W.C.[2], Zappia, J.[3], Morris, J.[1] [1]Loma Linda University Medical Center, Loma Linda, CA; [2]Loma Linda University Medical Center, Loma Linda, CA; [3]Loma Linda University Medical Center, Loma Linda, CA.

Background: Dasatinib is a second-generation abl tyrosine kinase inhibitor approved for patients with imatinib-intolerant or resistant CML and Ph+ ALL. Plasma PK has not been studied in children or CSF. **Methods:** Prospective analysis of dasatinib plasma and CSF levels and clinical response in an 8-year-old male with Ph+ ALL in relapse (diagnosed at age 6 y). Serum and CSF levels were determined by liquid chromatography tandem mass spectrometry with a detection limit of 1 ng/ml. **Results:** The patient received an unrelated donor stem cell transplant in 1st remission and a second transplant following relapse 6 mo later. He received Imatinib 300 mg po QD (15 mg/kg) during consolidation, maintenance, and following his 1st transplant. He developed headache, leg pain, and a single skin nodule of leukemia 7 mo after his last transplant. CSF had 7 blasts/ul, head CT showed hyper-intense chloromas in frontal, parietal, and temporal lobes, and a right ileopsoas mass. Bone marrow was in remission, peripheral blood had 0.15% BCR/ABL by RT-PCR. Dasatinib 40 mg po bid (1.5 mg/kg) was started. No other chemotherapy was given. Clinical symptoms resolved after 6 days. After 9 the CNS lesions became hypointense. Two large frontal lobe masses, 1 parenchymal and 1 extra-axial, decreased in volume from ~15 cc to 1.1 cc and CSF blasts to <1/ul. By day 23 the chloromas had nearly resolved and CSF blasts were 0 by day 34. The psoas mass resolved after 14 d. Plasma PK was measured 3 times, and CSF 6 times at various points after dose. CNS response varied with plasma level. Plasma levels after 7 d on 40 mg bid were slightly lower than expected from adult data, (AUC 146 ng-h/ml, Cmax 40.4 ng-h/ml, and $T_{1/2}$ 2.2 hours). CSF levels were not detected at any time point. On day 171 the patient developed disseminated adenovirus and died on day 178. Post mortem showed no leukemia in blood, marrow, or psoas muscle tissue by RT-PCR. There was microscopic perivascular leukemia cell infiltration in the frontal lobe, thalamus, and cerebellum. There was no evidence of CNS infection. **Conclusions:** In this child plasma PK was similar to results in adults. Ph+ leukemia in the CNS may respond to dasatinib despite very low drug levels in the CSF.

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SECOND ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR ACUTE LEUKEMIAS RELAPSING AFTER FIRST TRANSPLANT IN PEDIATRIC PATIENTS

Martinez, C., Verneris, M.R., Weigel, B.J., Kumar, A., Baker, K.S. University of Minnesota, Minneapolis, MN.

Recurrent leukemia is the most frequent indication for second allogeneic hematopoietic cell transplantation (HCT) in pediatric patients. However, there are few reports describing in detail the overall survival in children who undergo a second stem cell transplant procedure. We present our experience from the University of Minnesota describing the outcome of 23 patients with either acute lymphoblastic leukemia (ALL, n = 9) or acute myeloid leukemia/myelodysplastic syndrome (AML/MDS, n = 14) who had relapsed after a first HCT and received a second allogeneic transplant. The median age at the time of second transplant was 10 yrs for the AML/MDS patients and 6.8 yrs for the ALL patients. All of the ALL patients were in complete remission at time of second transplant, for the AML/MDS patients 6 were in remission and 8 had active leukemia at the time of second HCT. The mean time from first transplant to relapse for the ALL group was 406 days (range 0–729) and 619 days (range 20–4410) for the AML/MDS group. Five patients received a second HCT from the same donor source, 6 patients who had prior autologous HCT received an unrelated donor (n = 5) or related donor (n = 1) for their second HCT, and the remaining patients (n = 12) received a different allogeneic stem cell source. All of the patients except one patient with AML/MDS received myeloablative conditioning with the second HCT. Patients who received TBI with the first HCT were treated with chemotherapy only conditioning regimens and those who had not received TBI with the first HCT were treated with TBI based regimens for the second HCT. The mean follow-up of the patients with AML/MDS was 543 days (range 72–2109) and 708 days (range 23–2064) for the ALL group. The overall survival was 30% (n = 7), four of fourteen survived in the AML/MDS group and three of nine in the ALL group. Among the survivors the mean time from first