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A NOVEL ANTI-CD22 IMMUNOTOXIN, MOXETUMOMAB PASUDOTOX (HA22, CAT-8015): ACTIVITY IN PEDIATRIC PATIENTS WITH RELAPSED ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (SCT)

Shah, N.N.[1], Bhojwani, D.[2], Silverman, L.B.[3], Whitlock, J.A.[4], Richards, K.[1], Stetler-Stevenson, M.[5], Buzoianu, M.[6], Ibrahim, R.[6], Pastan, I.[7], Wayne, A.S.[1,7] [1]National Institutes of Health, Bethesda, MD; [2]St. Jude Children's Research Hospital, Memphis, TN; [3]Dana-Farber Cancer Institute/Children's Hospital Boston, Boston, MA; [4]Hospital for Sick Children, Toronto, ON, Canada; [5]National Institutes of Health, Bethesda, MD; [6]MedImmune, LLC, Gaithersburg, MD; [7]National Institutes of Health, Bethesda, MD

Background: Despite the curative potential of SCT for pediatric ALL, relapse remains the most frequent cause of treatment failure. Management of relapse after SCT is complicated by drug resistance, limited utility of DLI, treatment-related toxicities, and GVHD. Moxetumomab pasudotox (MP) is a recombinant anti-CD22 immunotoxin with properties that warrant evaluation in the peritransplant setting. Cytotoxicity is mediated by targeted inhibition of protein synthesis in CD22+ cells, an antigen expressed on most B-lineage ALL blasts, and no immune effector cells are required for activity.
Methods: A pediatric phase I trial of MP is being conducted for CD22+ hematologic malignancies (ClinicalTrials.gov NCT00659425). Doses are administered at 5-40 μg/kg IV QODx6 every 21 days. An initial cohort (A) included 1 patient each at the first 3 dose levels followed by standard 3+3 dose escalation starting at 30 μg/kg. In an attempt to prevent capillary leak syndrome (CLS), an ongoing cohort (B) receives dexamethasone around MP doses.
Results: 23 patients have been treated to date. The most common drug-related adverse events (AEs) were mild, reversible increased weight, transaminase elevation, and hypoalbuminemia. Treatment was discontinued in 1 patient after dose 1 due to ALL-related complications. Dose-limiting CLS was observed in 2 patients in Cohort A (30 μg/kg; grade 3 and 4, deemed drug-related serious AEs) and in no patients in Cohort B. 1 patient treated at 40 μg/kg developed refractory hypercalcemia, that was possibly drug-related, and died of cardiac arrhythmia during central venous catheter placement. That dose level (5B) was expanded and is accruing. 12 of 23 patients had prior SCT for ALL. Time from SCT to relapse was 3-12 mos (median, 9) and from SCT to treatment with MP was 4-34 mos (median, 13). 9 of 12 patients who had previously undergone SCT were evaluable for response. 3 (33%) patients had complete responses (CR) and 4 (44%) had hematological activity (>50% blast reduction and/or improvement in neutrophil/platelet counts). 1 patient with a CR confirmed by flow cytometry proceeded to 2nd SCT.
Conclusions: MP is active in relapsed pediatric ALL after SCT. Notably, 3 of 4 CRs observed so far on this trial have been in patients treated for post-transplant relapse. The observed antileukemic activity and safety profile of MP, coupled with its unique properties, warrant further study in the peritransplant setting.

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TREOSULFAN, FLUDARABINE AND ALEMTUZUMAB CONDITIONING FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN WITH PRIMARY IMMUNODEFICIENCY: UK EXPERIENCE

Slatter, M.[1], Rao, K.[2], Chiesa, R.[2], Amrolia, P.[2], Nademi, Z.[1], Flood, T.[1], Abinun, M.[1], Cant, A.[1], Hambleton, S.[1], Goulden, N.[2], Davies, G.[2], Qasim, W.[2], Gaspar, H.B.[2], Gennery, A.[1], Veys, P.[2] [1]Newcastle upon Tyne Hospital NHS Foundation Trust, Newcastle upon Tyne, United Kingdom; [2]Great Ormond Street Hospital NHS Trust, London, United Kingdom

Ninety-eight children received Treosulfan 42g/m^2 or 36g/m^2 (<1 year), Fludarabine 150mg/m^2 with Alemtuzumab (in most), prior to Hematopoietic Cell Transplantation (HCT) for Primary Immunodeficiency (PID) or Severe Immune Dysregulation between 2004 and July 2011.

Median age at transplant was 10 months (range: 1.4 to 191); 55% patients were 12 months or younger. Donors were: unrelated (79), of which 28 were cord blood (CB), matched sibling donors (3), other matched family donors (13), haploidentical donors (3). Stem cell source was: PBSC (39), BM (31), CB (28). Median follow up was 18.5 months (range: 2 to 82).

Overall survival was 85%. Of the 15 deaths, 8 patients had HLH many of whom were not in remission at the time of HCT. There was no VOD and no toxicity related deaths. Eighteen % had GVHD, only 7% > grade II. One patient rejected their graft; 35 of 55 (64%) more than 1 year post transplantation had 100% donor chimerism in all cell lineages. Increased use of PBSC favoured improved donor myeloid chimerism and with the use of Alemtuzumab the incidence of significant GVHD was not increased. High levels of donor chimerism are of particular importance in diseases such as Wiskott Aldrich Syndrome and Chronic Granulomatous Disease.

Long-term follow up is required to determine the gonadotoxic effects of this approach in comparison to Busulfan containing regimens, but the combination of Treosulfan, Fludarabine and Alemtuzumab is an ideal choice of conditioning for HCT in PID, associated with good lymphoid and myeloid engraftment and low regimen related toxicity.

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EARLY HEMATOPOIETIC STEM CELL TRANSPLANT IS ASSOCIATED WITH IMPROVED OUTCOMES IN CHILDREN WITH MDS

Christiansen, E.C.[1], Trotz, B.A.[2], Cao, Q.[3], Lipsitz, E.[2], Weigel, B.J.[2], Stefanski, H.E.[4], Verneris, M.R.[4], Burke, M.J.[2], Smith, A.R.[4] [1]University of Minnesota, Minneapolis, MN; [2]University of Minnesota, Minneapolis, MN; [3]University of Minnesota, Minneapolis, MN; [4]University of Minnesota, Minneapolis, MN

Background: Childhood myelodysplastic syndrome (MDS) is a rare, heterogeneous disorder that is clinically distinct from adult MDS. Hematopoietic stem cell transplant (HSCT) is the treatment of choice, but there is no consensus regarding patient, disease, or treatment-related factors that predict outcomes after HSCT.
Materials and Methods: We performed a retrospective review of 37 consecutive pediatric patients who received allogeneic HSCT for MDS at the University of Minnesota Amplatz Children's Hospital between 1990 and 2010.

Table. Patient Characteristics

	Total (%)
Total Patients	37
Gender	
Male	18 (49%)
Female	19 (51%)
Median Age at Diagnosis	11 (range 1-21)
Year of HSCT	
1990-1999	24 (65%)
2000-2010	13 (35%)
Time from Diagnosis to HSCT (days)	
<140	18 (49%)
≥140	19 (51%)
Type of MDS	
Primary	20 (54%)
Secondary	17 (46%)
Blast Count Pre-HSCT	
<5%	27 (73%)
≥5%	10 (27%)
Cytogenetics*	
Monosomy 7	21 (57%)
Trisomy 8	7 (19%)
Normal/Other	8 (22%)
MDS Classification	
RC	30 (81%)
RAEB	7 (19%)
IPSS Risk	
Low	1 (3%)
Int-1	15 (40%)
Int-2	21 (57%)
Pre-HSCT Chemotherapy	

(*Continued*)

Table. (*Continued*)

	Total (%)
Yes	6 (16%)
No	31 (84%)
Myeloablative Conditioning	37 (100%)
Graft Source	
UCB	9 (24%)
MRD	15 (41%)
MURD	7 (19%)
MMURD	6 (16%)
HLA Match	
Match	20 (54%)
Mismatch	17 (46%)
CSA containing GVHD Prophylaxis	
Yes	29 (78%)
No	8 (22%)

*Cytogenetics not available for 1 patient

Results: Neutrophil engraftment occurred in 89% of patients at a median of 23 days (range 12-40). Patients transplanted after year 1999 were more likely to engraft (RR 2.27, p = .04). Overall survival (OS) was 70% and 53% at 1 and 3 years. In multivariate analysis (MVA), OS was increased in patients who did not receive pre HSCT chemotherapy (RR 0.04, p = .01) and decreased in those with an IPSS score of Int-2 (RR 11.96, p = .03). Disease free survival (DFS) was 62% and 48% at 1 and 3 years. In MVA, factors associated with improved DFS at 3 years include having secondary MDS (RR 0.13, p = .02), undergoing HSCT after 1999 (p = .02 at 3 years), not receiving pre HSCT chemotherapy (RR 0.06, p<.01), and a short interval (<140 days) from diagnosis to transplant (RR 0.21, p = .03). Those with an IPSS score of Int-2 had a significantly lower DFS (RR 3.96, p = .03). WHO classification, cytogenetics and pre HSCT blast percentage had no significant impact on either OS or DFS. The relapse rate at 2 years was 20%. Factors associated with decreased relapse include having secondary MDS (RR 0.04, p<.01) and not receiving pre HSCT chemotherapy (RR 0.21, p = .03). Treatment-related mortality (TRM) was 25% at 1 year. The risk of TRM was increased in patients with a pre HSCT blast count ≥ 5% (RR 6.65, p = .01) and was decreased in patients who did not receive pre HSCT chemotherapy (RR 0.07, P = .02). At 100 days the cumulative incidence of grades II-IV and III-IV acute graft versus host disease (GVHD) was 40% and 16%, respectively. The incidence of chronic GVHD at one year was 19%.

Conclusions: Our results suggest that in order to achieve optimal outcomes, children with MDS should be referred for allogeneic HSCT soon after diagnosis and that unlike in adult MDS, pre HSCT chemotherapy does not appear to improve outcomes.

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OUTCOME OF POOR RESPONSE PAEDIATRIC AML USING EARLY SCT

Wareham, N.E.[1], Heilmann, C.[1], Abrahamsson, J.[2], Forestier, E.[3], Gustafsson, B.[4], Ha, S.-Y.[5], Heldrup, J.[6], Jahnukainen, K.[7], Jónsson, Ó.G.[8], Lausen, B.[1], Palle, J.[9], Zeller, B.[10], Hasle, H.[11] [1] The University Hospital Rigshospitalet, Copenhagen, Denmark; [2] The Queen Silvia Children's Hospital, Gothenburg, Sweden; [3] University of Umeå, Umeå, Sweden; [4] Karolinska Institute, Karolinska University Hospital, Huddinge, Sweden; [5] Queen Mary Hospital, Hong Kong; [6] University Hospital Lund, Lund, Sweden; [7] Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland; [8] University Hospital, Reykjavík, Iceland; [9] University Children's Hospital, Uppsala, Sweden; [10] Oslo University Hospital Rikshospitalet, Oslo, Norway; [11] Aarhus University Hospital Skejby, Aarhus, Denmark

Background: Children with poor response acute myeloid leukaemia (AML) or refractory AML are generally considered to have a very poor outcome. Allogeneic stem cell transplantation (SCT) has been recommended for these children however, the advantage of SCT as opposed to continuous chemotherapy is not clear. The aim of this study was to investigate survival for poor response AML patients treated with SCT.

Procedure: The patients were treated according to the NOPHO-AML 2004 protocol and data were collected from the NOPHO-AML database. All patients received AIET (Cytarabine, Idarubicin, Etoposide, Thioguanine) and AM (Cytarabine, Mitoxantrone) as induction therapy. Poor response was defined as more than 15% blasts on day 15 after AIET and/or >5% blasts after AM. These patients proceeded to allo-SCT if a donor (family or unrelated) was available.

Results: Twenty-five of 230 patients had a poor response. SCT was performed in 21, using unrelated donors in 16, matched sibling donors (MSD) in 4 and a haploidentical donor in one of the transplants. The median follow-up was 2.9 years (range 0.7-7.3) and 3-year probability of survival 89%. Of five patients with more than 5% blasts at time of SCT four remain alive.

Conclusions: The poor responders had a significantly better prognosis than has previously been reported for patients with high blast count on day 15 and it seems that SCT is the treatment of choice for children with poor response AML.

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EGF SIGNALING REGULATES HEMATOPOIETIC REGENERATION FOLLOWING TOTAL BODY IRRADIATION

Doan, P.L.[1], Russell, J.L.[1], Himburg, H.A.[1], Helms, K.[1], Sullivan, J.M.[2], Jeffords, L.B.[2], Chao, N.J.[1,4], Kirsch, D.G.[2,3], Chute, J.P.[1,3] [1] Duke University Medical Center, Durham, NC; [2] Duke University Medical Center, Durham, NC; [3] Duke University Medical Center, Durham, NC; [4] Duke University Medical Center, Durham, NC

VEGFR2+ sinusoidal endothelial cells are necessary for normal hematopoietic reconstitution following myelosuppressive chemo- or radiotherapy (Hooper et al, Cell Stem Cell 2009). However, the mechanisms through which BM endothelial cells promote HSC regeneration remain unknown. We developed a mouse model in which mice bearing cell-specific deletion of Bak and Bax in Tie2$^+$ cells (Tie2Cre;Bak1-/-;BaxFl/- mice) were irradiated with sublethal and lethal doses of total body irradiation to assess whether protection of BM Tie2$^+$ ECs from radiation-induced apoptosis could protect the hematopoietic compartment from myeloablative toxicity. Tie2Cre;Bak1-/-;BaxFL/- mice demonstrated protection of BM HSCs and 100% survival following lethal dose TBI (750 cGy), whereas mice that retained Bax expression in Tie2$^+$ cells demonstrated depletion of BM HSCs and only 10% survival (p<0.0001). To determine the mechanism through which Tie2$^+$ BM ECs regulate HSC regeneration, we performed a cytokine array screen of BM serum from Tie2Cre;Bak1-/-;BaxFl/- mice and compared with Tie2Cre;Bak1-/-;BaxFl/+ mice and C57Bl6 mice. Among several genes which were up- or down-regulated in the BaxFl/- mice, we found an 18-fold increase in the concentration of epidermal growth factor (EGF) compared to BaxFl/+ and C57Bl6 mice (p = 0.04). We then showed that BM ECs express EGFR and BM ckit+sca-1+lin- cells also express EGF in C57Bl6 mice. Interestingly, antibody blockade of EGF in vitro blocked the ability of BaxFl/- ECs to support HSC regeneration following 300 cGy irradiation. Furthermore, systemic administration of EGF to irradiated mice caused a profound recovery of BM HSC and progenitor cells compared to saline treated control mice. Similarly, administration of erlotinib, an EGFR antagonist, caused a significant delay in recovery of BM HSCs in mice following high dose irradiation. Mechanistic studies revealed that treatment of HSCs with EGF significantly increased EGFR phosphorylation and downstream activation of Akt signaling. Furthermore, inhibition of Akt signaling blocked the beneficial effect of EGF in mediating the recovery of HSCs following radiation exposure, suggesting that EGF action on HSC regeneration was mediated by Akt activation. These data demonstrate that EGF is an important regulator of HSC regeneration in vivo and a potential new target for therapies to accelerate hematopoietic reconstitution following chemotherapy and radiation exposure.