Appendix I – Select Poster Presentations
2013 American Society of Hematology (ASH) Annual Meeting Updates
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Conditioning Regimens

Abstract 3280 – Pharmacokinetics of a Generic Formulation of Intravenous Busulfan (BUCELON 60™) in Patients Undergoing Hematopoietic Stem Cell Transplantation (Mohanan E, et al. *Blood.* 2013;122(21):3280)

- Background
  - High-dose IV busulfan is widely used as part of conditioning regimens for HCT
  - Busulfan has a narrow therapeutic index with significant toxicity at high systemic exposure (P Ljungman *Bone Marrow Transplant* 1997) and graft rejection at low systemic exposure (AM Bolinger *Bone Marrow Transplant* 2001)
  - Wide interpatient variability in busulfan exposure is seen with oral administration due to unpredictable GI absorption and differences in hepatic metabolism
    - Polymorphisms have been identified in some patients to explain observed differences in pharmacokinetic parameters in some conditions (Srivastava *Blood* 2004, B Poonkuzhali 2011 ASH Annual Meeting)
  - Targeted IV busulfan has resulted in reliable systemic exposure owing to its predictable pharmacokinetics, while minimizing toxicity and treatment failure
    - Generic formulation of busulfan has not been studied to date
- Objectives
  - Document the PK of a generic formulation of IV busulfan
  - Evaluate the role of generic IV busulfan on transplant outcome
- Methods
  - Patients
    - 95 patients with various hematologic disorders treated between June 2010 and July 2013 included for analysis
      - 73 patients – 130 mg/m^2/dose Q 24 hours
      - 22 patients – 0.8 mg/kg/dose Q 6 hours
  - Sampling
    - Day 1 and Day 3 measurements of peripheral blood
      - Q 24 hr – at hours 0, 3, 4, 5 and 7
      - Q 6 hr – at hours 0, 2, 3, 4 and 6
  - Analysis
    - By LC-MS/MS method (Desire *IJMR* 2013)
    - AUC targets
      - Q 24 hr – 20,000-22,000 microMol*min
      - Q 6 hr – 900-1350 microMol*min
    - Polymorphism screening using PCR-RFLP
      - GSTA1, GSTM1, GSTT1, GSTP1
      - CYP2B6, CYP2C19, CYP3A4
  - Modeling
    - POPPK model was developed using NONMEM software to evaluate the effect of demographic and pharmacogenetic factors on the PK of IV busulfan

        - Effect of busulfan first dose AUC on the toxicity and outcome post HCT was evaluated
- Results
    - Patient demographics
        - Q 24 hr (73 patients)
            - Median age = 32 years (1-61.4 years)
            - Gender = 45 males and 28 females
            - Median weight = 58.6 kg (8.8-104.2 kg)
            - Median BSA = 1.63 m^2 (0.38-2.11 m^2)
        - Q 6 hr (22 patients)
            - Median age = 4 years (1-14 years)
            - Gender = 13 males and 9 females
            - Median weight = 14.4 kg (4.4-31 kg)
            - Median BSA = 0.61 m^2 (0.47-1.08 m^2)
            - Of note – all were patients diagnosed with thalassemia
    - Busulfan kinetic parameters
        - Q 24 hr
            - First dose of busulfan – 210 mg (32-275 mg)
            - 1st dose AUC – 4180 microMoles*min (1713-10456 microMoles*min)
            - Clearance – 41.83 L/hr (2.47-144.84 L/hr)
            - Volume – 156.3 L (6.5-454.51 L)
        - Q 6 hr
            - First dose of busulfan – 11.8 mg (8.4-24.6 mg)
            - 1st dose AUC – 603 microMoles*min (307-1456 microMoles*min)
            - Clearance – 4.19 L/hr (0.81-21.55 L/hr)
            - Volume – 17.56 L (2.51-243.9 L)
        - Busulfan dose adjustments
            - Doses adjusted at the 2nd and 3rd dose for the Q 24 hr and Q6 hr regimens, respectively to achieve the target AUC
                - 26% of doses decreased
                - 13% of doses had no change
                - 61% of doses increased
            - Dose adjustments never exceeded 20%
            - Out of 95 patients, 43% required further adjustments on Day 4 to achieve target AUC
        - Median Day1 busulfan AUC achieved with generic IV busulfan in this study (for both Q 24hr and Q 6hr was lower compared to previous reports with IV Busulfex®
            - Q 24 hr – see Russell 2002 vs. this report
                - Busulfan AUC, mg/L/hr
                    - Mean $\pm$ SD – 4866.51 $\pm$ 771.42 vs. 4609.39 $\pm$ 1760.89
                    - Median (Range) – 4972 (3431.68-6244.48) vs. 4180 (1713-10456)
            - Q 6 hr – see Lucarelli 2010 vs. this report
                - Median age – 9 years (1.6-27 years) vs. 4 years (1-14 years)
                - Busulfan AUC, micromole*min
                    - Mean $\pm$ SD – 996 $\pm$ 213 vs. 708 $\pm$ 304
                    - Median – 971 (630-1621) vs. 603 (307-1456)
                - Busulfan clearance, mL/min
                    - Mean $\pm$ SD – 4.15 $\pm$ 0.87 vs. 5.67 $\pm$ 4.62
                    - Median – 4.10 (2.38-6.19) vs. 4.17 (0.51-21.55)
    - Since wide inter-individual variation was observed in these patients, a POPPL model was developed incorporating demographic, biological, biochemical and genetic variables
        - In addition to weight and age, GSTA1 polymorphism was found to be one of the covariates which explained the inter-patient variation
        - When the weight normalized model was considered, the Cl and Vd decreased with weight. Clearance was also higher in individuals with GSTA1 wild type genotype.

        - Weight normalization explained 45% and 56% of the inter-patient variation variability on Cl and Vd, respectively
    - Toxicity
        - Neither toxicity or rejection/relapse was significantly associated with busulfan systemic exposure
            - 10% SOS
            - 13% GVHD (Grade III-IV)
            - 13% Rejection/failure to engraft/relapse
- Conclusions
    - First report of PK of generic formulation of IV busulfan
    - Majority of patients required an increase in busulfan dose
    - No significant association between 1st dose PK parameters and toxicity or rejection
    - The main covariates found to influence the inter-patient variability PK parameters were body weight, age, and GSTA1 polymorphism
    - When compared to previous reports, systemic exposure to generic IV busulfan was lower, strongly suggesting the need for targeted-dose adjustments when using this product during HCT conditioning
    - Lower busulfan systemic exposure could be due to population difference, drug formulation or a combination of both

Abstract 3281 – Impact of Renal Insufficiency and Obesity on Safety and Outcomes of BEAM Conditioning (Afifi S, et al. *Blood.* 2013;122(21):3281)

- Background
    - BEAM (carmustine, etoposide, cytarabine, melphalan) is a standard conditioning regimen for patients with NHL undergoing auto-HCT
    - Guidelines do not exist to address the dosing of these agents in patients with renal dysfunction or obesity (practices vary among centers)
    - Institutional practice of investigators is to administer BEAM without dose reduction regardless of BMI or modest renal insufficiency
- Objectives
    - Determine the effect of impaired renal function or obesity on the toxicities associated with full-dose BEAM conditioning and the outcomes related to auto-HCT in a retrospective analysis
- Methods
    - Analysis of lymphoma patients treated with BEAM followed by auto-HCT at Memorial Sloan Kettering Cancer Center between September 2003 and December 2011
    - Collection of data from electronic medical records
        - Dose of BEAM
        - Number of prior chemotherapy regimens
        - Hematopoietic stem cell transplant comorbidity index (HSCT-CI)
        - Pre-transplant CrCl (as per Cockcroft-Gault equation)
        - BMI
        - Toxicities: mucositis, febrile neutropenia, infection, renal dysfunction, hepatoxicity, pulmonary toxicity and heart failure requiring inotropic support
        - LOS for HCT admission
        - Time to neutrophil and platelet engraftment
        - Relapse and mortality up to December 2011
    - Statistical analysis
        - Uni-and multivariate analysis for associations between baseline CrCl/BMI and age, histology, prior therapy, disease response and HSCT-CI
        - Logistic regression for toxicity endpoints
        - Linear regression and ANOVA for LOS
        - Cox regression model and Gray's competing risks for OS and relapse risk
- Results
    - Baseline characteristics (343 patients)

        - Age, median (range) – 56 years (17-73 years)
        - CrCl, median (range) – 92.3 mL/min (28.6-207.7 mL/min)
            - 12% had CrCl in the range of 30-59 mL/min
        - BMI, median (range) – 27.6 kg/m2 (15.8-47.1 kg/m2)
            - 33% were obese
                - 12% had BMI 35-39 and 3% had BMI of $\geq$ 40
        - Malignancy – 42% DLBCL, 34% MCL, 12% T-cell NHL and 12% other
        - Dose of BEAM
            - 63% - B 300 x 1, E 100 x 8, A 100 x 8, M 140 x 1
            - 29% - B 300 x 1, E 100 x 8, A 200 x 8, M 140 x 1
            - 5% - B 300 x 1 , E 150 x 8, A 200 x 8, M 140 x 1
        - HSCT-CI – 86% 0-3, 14% $\geq$ 4
    - End organ damage
        - Renal insufficiency (30-59 mL/min) had a statistical effect in both uni- and multivariate analysis
        - BMI $\geq$ 30 had a statistical effect in multivariate analysis only (with a BMI 25-29 trending towards statistical significance in multivariate analysis)
    - Length of stay
        - Moderate renal insufficiency (30-59 mL/min) had a statistical effect in both uni- and multivariate analysis
        - BMI 25-29 had a statistical effect in the univariate analysis
    - Toxicity
        - Mucositis and F/N were not associated with renal insufficiency or obesity
    - Engraftment of neutrophils was not associated with renal insufficiency or obesity
    - Outcomes
        - Renal insufficiency, BMI and dose of beam did not affect relapse-free survival
        - Only renal insufficiency (30-59 mL/min) had a statistical effect on overall survival
    - Day 100 mortality
        - In relation to CrCl
            - 2% if $\geq$ 60 mL/min vs. 5% if < 60 mL/min (P=NS)
        - Causes – 3 cardiac or respiratory arrest; 3 cancer-related; 2 unknown
- Conclusions
    - Patients with renal insufficiency or obesity experience increased risks of acute organ damage, those with renal insufficiency have inferior OS, but Day 100 mortality remains low in both groups
    - Authors findings do not support routine dose adjustments of BEAM for obesity or moderate renal insufficiency

Abstract 2170 – Use of Biosimilar G-CSF Compared with Lenograstim in Autologous Haematopoietic Stem Cell Transplant and in Sibling Allogeneic Transplant (Agrawal S, et al. *Blood.* 2013;122(21):2170)

- Background
    - Biosimilars of filgrastim have been available since 2008 and are widely used clinically in Europe and elsewhere (P Gascon *Support Care Cancer* 2013)
    - Several studies have shown biosimilar filgrastim is comparable to original filgrastim when used for HCT (F Lefrere *Adv Ther* 2011; JC Ianotto *Bone Marrow Transplant* 2012)
    - Lenograstim (a glycosylated GCSF) is also widely used in HCT
        - Differences with mobilization when compared to original filgrastim (IH Kim *Curr Med Res Opin* 2003, R Ria *Bone Marrow Transplant* 2010)
        - But some studies have reported comparable efficacy (F Lefrere *Leuk Lymph* 1999, S Ataergin *Am J Hematol* 2008, O Perez-Lopez *Transfusion* 2013)
- Objectives
    - Compare biosimilar filgrastim with lenograstim for auto-HCT in patients with lymphoma or multiple myeloma (MM)
    - Report the use of biosimilar filgrastim for mobilization in sibling allo-HCT
- Methods

- Comparison of data in lymphoma and MM patients undergoing auto-HCT that were mobilized with biosimilar filgrastim between October 2011 and April 2013 at St. Bartholomew's Hospital (London, UK) to a historical control group undergoing a similar mobilization protocol using lenograstim between January 2009 and September 2011
    - Peripheral blood counts (WBC, CD34+ cells) monitored after 7-8 consecutive days of therapy
    - Apheresis performed on Day 8 if CD34+ cell count was $\geq$ 10 cells/microL
    - Stem cell collection goals
        - $\geq 2 \times 10^6$/kg for lymphoma
        - $\geq 4 \times 10^6$/kg for MM (patients $\geq$ 60 years old – "older patients")
        - $\geq 8 \times 10^6$/kg for MM (patients < 60 years old – "younger patients")
  - Data sibling donors collected as well for patients undergoing allo-HCT for hematologic malignancies between October 2010 and April 2013
- Results
  - Auto-HCT
    - 259 patients (103 received biosimilar filgrastim and 156 lenograstim)
        - Groups well balanced except biosimilar group had lower percentage of patients with lymphoma
    - In patients with lymphoma and older patients with MM, no significant differences in stem cell mobilization parameters measured
    - In younger MM patients, all parameter favored the use of biosimilar filgrastim compared to lenograstim, including the need for one rather than two sessions of apheresis
    - Among those patients proceeding to transplant, no significant differences were observed between biosimilar filgrastim and lenograstim in terms of neutrophil and platelet recovery
  - Allo-HCT
    - 48 sibling donors received biosimilar filgrastim
    - Mean CD34+ cell count at the 1st session of apheresis was 6.1×10^6/kg
    - 13 donors required a 2nd session of apheresis; 4 donors needed a 3rd
    - Among recipients, median recovery time was 16 days (10-28 days) for ANC and 13 days (9-54 days) for platelets
- Conclusions
  - Biosimilar filgrastim is as effective as lenograstim for auto-HCT in patients with lymphoma or MM patients $\geq$ 60 years old
  - In younger MM patients (< 60 years), all mobilization factors (peripheral WBC and CD34+ cell counts, total CD34+ cells collected, peripheral blood stem cell harvest WBC, number of apheresis sessions) appeared to favor biosimilar filgrastim compared with lenograstim
  - Biosimilar filgrastim was also successfully used to mobilize hematopoietic stem cells in sibling donors for allo-HCT

Abstract 3275 – The Use of Tevagrastim (Biosimilar Filgrastim XMO2) for Hematopoietic Stem Cell Mobilization in HLA Matched Sibling Donors For Allogeneic Stem Cell Transplantation to AML/MDS Patients (Nagler A, et al. *Blood.* 2013;122(21):3275)

- Background
  - Human recombinant G-CSF (filgrastim) has been widely used for mobilization of CD34+ cells from healthy donors but the experience with biosimilar filgrastim is limited
- Objective
  - Prospectively study the tevagrastim for mobilization of CD34+ peripheral blood hematopoietic stem cells in healthy sibling donors of patients with AML/MDS
- Methods
  - Tevagrastim 10 microgram/kg SQ BID x 4 days given to donors of 24 patients with AML or high-risk MDS
    - Target yield was 5×10^6 CD34+ cells/kg body weight of recipient
  - Recipient conditioning
    - Myeloablative Bu/Cy = 10
    - Reduced toxicity (Flu/Treosulfan, Flu/Bu4) = 10

        - Reduced intensity Flu/Bu2 = 4
- Results
    - Efficacy
        - Median number of CD34+ cells/kg collected: 10.2 x 10^6 (0.93-35.4 x 10^6)
        - Median number of CD3+ cells/kg collected: 4.4 x 10^8 (1.74-11.6 x 10^8)
        - Mean number of apheresis procedures: 1.3
    - Engraftment
        - ANC > 500: median 13 days (10-21 days)
        - Platelets > 20 x 10^9/L: within a median of 16 days (12-33 days)
    - Transplant related toxicity
        - Mucositis in 15 patients (9 with grade II and 6 with grade III-IV)
        - Infection complications in 20 patients
        - Fluid retention in 8 patients
        - VOD – 1 patients with grade 1
        - aGVHD – 5 with grade II-III
        - TRM (Day 100) 4.2% (1 of 24 patients)
        - Leukemia progression in 2 patients
    - Safety
        - Transient arthralgias in 12 of 24 donors
        - Flu-like syndrome in 2 of 24 donors
- Conclusion
    - Tevagrastim appears safe and efficient for stem cell mobilization in HLA-matched healthy sibling donors
    - The yield of CD34+ and CD3+ cells, the number of apheresis sessions, and engraftment measurements with tevagrastim are similar to those seen in historical controls using filgrastim
    - Neither graft rejection nor side effects (in both recipients and donors) occurred more frequently than expected from filgrastim

Graft-versus-Host Disease

Abstract 3297 – Higher Mycophenolic Acid (MPA) Trough Levels Result in Lower Day 100 Severe Acute GVHD Without Increased Toxicity in Double-Unit Cord Blood Transplantation (CBT) Recipients (Harnicar S, et al. *Blood.* 2013;122(21):3297)

- Background
    - Therapeutic monitoring of mycophenolic acid (MPA), the active metabolite of mycophenolate mofetil (MMF), is advisable due to the intra- and inter-patient variability of MMF pharmacokinetics
    - Increased incidence of aGVHD has been associated with low unbound MPA AUCs in HCT recipients
    - AUCs are cumbersome to measure, thus a limited pharmacokinetic parameter such as MPA troughs would be better to measure
    - Toxicity associated with MPA trough levels is not established and is of concern in UCBT, particularly due to the theoretical risk of myelosuppression resulting from high MPA levels
- Objectives
    - Describe MPA total serum trough levels in weeks 0-6 of UCBT recipients
    - Correlate trough levels in weeks 0-6 of transplant with toxicity as measured by neutrophil and platelet engraftment, resolution of GI toxicities and time to CMV reactivation
    - Correlate trough levels in weeks 0-6 of transplant with efficacy as measured by onset of aGVHD (grade II-IV and III-IV) within the first 100 days after transplant
- Methods
    - Evaluation of both pediatric and adult double-cord blood transplant recipients between August 2009 and June 2012
        - Transplanted for hematologic malignancies
        - 4-6/6 HLA-A, -B antigen, -DRB1 allele matched cord blood grafts
    - MMF dosing
        - Prior to April 2010 – Q 12 hr dosing with patients < 12 years receiving 15 mg/kg/dose

        - After April 2010
            - 1 gm IV Q 8 hrs if both > 12 years and ≥ 50 kg
            - 15 mg/kg IV Q 8 hrs if > 12 years and < 50 kg
            - 20 mg/kg IV Q 8 hrs (max 1 gm IV Q 8 hrs) if < 12 years
    - Trough levels dichotomized
        - Toxicity: < 2 mcg/mL vs. ≥ 2 mcg/mL
        - Efficacy: < 0.5 mcg/mL vs. ≥ 0.5 mcg/mL
- Results
    - Patient characteristics (83 patients)
        - Age, mean (range) – 39 years (1-71 years)
            - 20% were < 16 years old
        - Gender – 58% male
        - Primary disease – 61.4% ALL, 30.2% NHL/HL/CLL
        - CR at the time of UCBT – 78.3%
        - High risk patients – 88%
        - Conditioning – 83% myeloablative
        - CMV seropositive – 54%
    - Trough levels
        - Younger age (< 16 years) was associated with lower values (p=0.002)
        - Recipients of myeloablative conditioning had lower MPA troughs (p=0.02)
        - Median and range of MPA levels increased over time (p=0.03)
    - Toxicity
        - There was no association with trough values and time to neutrophil recovery, duration of TPN and time to viremia in CMV seropositive patients undergoing myeloablative conditioning
        - Myeloablative UCBT recipients with MPA troughs ≥ 2 mcg/mL had enhanced platelet recovery compared to those patients with lower trough values (p=0.005)
    - aGVHD – Cumulative incidence at Day 100
        - Grade II-IV
            - MPA trough < 0.5 mcg/mL = 61% (95% CI: 37-85)
            - MPA trough ≥ 0.5 mcg/mL = 57% (95% CI: 45-70) (p=0.52)
        - Grade III-IV
            - MPA trough < 0.5 mcg/mL = 28% (95% CI: 6-49)
            - MPA trough ≥ 0.5 mcg/mL = 10% (95% CI: 2-17) (p=0.06)
- Conclusions
    - Analysis suggests higher total MPA serum trough levels are safe and may protect against the development of aGVHD
    - Beneficial effect on platelet engraftment was not expected and may be explained by a lower incidence of severe aGVHD
    - Prospective investigation is warranted

Abstract 4571 – A Pilot Study of Continuous Infusion Mycophenolate Mofetil for Graft Versus Host Disease Prophylaxis (Goyal R, et al. *Blood.* 2013;122(21):4571)

- Background
    - Mycophenolate mofetil (MMF), an ester prodrug of mycophenolic acid (MPA), has been successfully used for GVHD prophylaxis
    - Pharmacokinetic parameters and dosing regimens have been established in solid organ transplant recipients but data remains limited in HCT patients
    - Empiric fixed-dose-escalation strategies have failed to achieve target MPA exposure, especially in the early period following conditioning therapy.
    - Authors hypothesized that a PK-based dosing approach using a novel continuous infusion (CI) method of MMF will be able to achieve and maintain target MPA exposure
- Objective

- Evaluate the safety and feasibility of AUC-based MMF targeting for GVHD prophylaxis in pediatric patients undergoing myeloablative conditioning

- Methods
  - Eligible patients were children (6 months-21 years old) undergoing allo-HCT at Children's Hospital of Pittsburgh (exclusion criteria included" prior HCT, mismatched donor, peripheral blood as a stem cell source, reduced-intensity conditioning, uncontrolled infections and poor organ function)
  - GVHD prophylaxis
    - Cyclosporine as a continuous IV infusion starting on Day -2 with a target blood level of 160-250 ng/mL)
    - MMF
      - IV started on Day 0 at 15 mg/kg/dose Q 8 hours
      - 1st PK samples were collected after a minimum of 5 IV doses → MMF converted to CI to target MPA AUC_{0-24} of 40-80 mcg/mL/hr
      - MMF doses adjusted to maintain a total MPA C_{ss} of 1.7-3.3 mcg/mL
      - When patients tolerated oral medications, CI MMF converted to Q 8 hr dosing regimen
      - 2nd PK study performed after a minimum of 5 oral doses → dose adjustments made to maintain a total MPA C_{trough} of 1-3.5 mcg/mL
      - MMF continued until Day +42 and in the absence of aGVHD, was tapered off over 8 weeks

- Results
  - 15 patients studied
    - Median age: 8.4 years (2-21.5 years)
    - Gender: 8 males, 7 females
    - Diagnosis: 9 ALL, 4 AML/Therapy-related MDS, 1 congenital erythropoietic porphyria, 1 severe congenital neutropenia
    - Stem cell source & HLA matching
      - 7 sibling BM (all HLA-identical)
      - 4 MUD BM (all A, B, C, DRB1, DQB1 matched)
      - 4 UCB (A, B, C, DRB1 – 1 matched and 3 mismatched)
    - Conditioning regimen
      - 8 Cy + TBI $\pm$ other
      - 7 Bu + Cy $\pm$ other
  - Total MPA pharmacokinetic parameters (mean $\pm$ SD)

	Intermittent IV	Continuous Infusion	Oral
MMF dose	15 $\pm$ 0 mg/kg/dose Q 8 hr	44 $\pm$ 16 mg/kg/24 hr	15 $\pm$ 6 mg/kg/dose TID
Half-life (hrs)	1.8 $\pm$ 1.3	---	2.6 $\pm$ 2.2
Vd (L/kg)	3.5 $\pm$ 3.6	---	4.0 $\pm$ 6.3
Cl (mL/min/kg)	14.1 $\pm$ 9.6	15.7 $\pm$ 9.1	15.4 $\pm$ 6.8
AUC_{0-24} (mg*hr/L)	50.1 $\pm$ 23.2	41.8 $\pm$ 12.6	43.9 $\pm$ 19.4
C_{ss} (mg/L)	---	1.7 $\pm$ 0.5	---
C_{max} (mg/L)	6 $\pm$ 2.2	---	6.5 $\pm$ 3.0

  - Adverse effects
    - MMF discontinued in 4 patients without weaning
      - 3 patients due to delay in blood count recovery (all of whom engrafted)
      - 1 patient due to suspected GI toxicity (later diagnosed with severe aGVHD)
  - Engraftment
    - All patients achieved neutrophil engraftment 13 $\pm$ 11 days post-HCT and platelet engraftment 45 $\pm$ 72 days post-HCT

        - One patient with severe congenital neutropenia developed autologous hematopoietic recovery by Day +52
    - aGVHD
        - 7 out of 15 (47%) patients developed stage I-IV aGVHD
        - 3 out of 15 (20%) patents had stage III-IV GVHD – all steroid-refractory but went into remission with additional therapy
    - cGVHD
        - For the 11 patients with a minimum of 1-year follow-up, 1 (9%) developed overlap cGVHD
    - Survival
        - 1 patient with ALL died of relapse on Day +150
        - Median follow-up of 27 months (211 days – 3.9 years), 14 of 15 patients are alive
        - 1-year EFS = 83% and 1-year OS = 92%
- Conclusions
    - CI MMF is feasible and well-tolerated
    - On this pilot PK study, the investigators observed no toxic deaths, excellent engraftment, and low rates of grade III-IV aGVHD and cGVHD
    - PK studies showed significantly shorter half-life and higher drug clearance in these patients compared to stable pediatric renal transplant patients
    - This regimen deserves further validation in a larger cohort of pediatric patients undergoing myeloablative HCT

Abstract 2067 – Tocilizumab in the Treatment of Steroid Refractory Graft Versus Host Disease: A Single Institutional Experience (Roddy J, et al. *Blood.* 2013;122(21):2067)

- Background
    - aGVHD is a frequent complication after HCT associated with significant transplant-related morbidity and mortality
    - aGVHD is fueled by the release of pro-inflammatory cytokines with subsequent decline of anti-inflammatory cytokines and T-regulatory cells (T-regs) leading to damage of host tissues
    - First-line treatment with corticosteroids produces a CR 30-40%
    - IL-6 is a pleiotropic cytokine that is reportedly elevated in the serum of patients with aGVHD
        - Tocilizumab is a humanized anti-IL-6 receptor (IL-6R) monoclonal antibody that inhibits IL-6-mediated pro-inflammatory activity
        - Small case series have shown encouraging activity (ORR 67%) for steroid-refractory GVHD
- Methods
    - Objective = evaluate response and safety of tocilizumab in patients with steroid-refractory aGHVD
        - Steroid-refractory defined as
            - No response after at least 1 week of high-dose steroids (2 mg/kg/day) OR
            - Progression after at least 72 hours of treatment with high-dose steroids
    - Tocilizumab 8 mg/kg IV every 2-3 weeks
    - aGVHD response determined by the International Bone Marrow Transplant Registry (IBMTR) scoring system
    - Toxicity assessed using the NCI CTCAE (version 4)
    - Patients monitored for infections according to institutional guidelines
- Results
    - N=9
    - Patient characteristics
        - Age range = 25-62 years
        - Gender = 5 males and 4 females
        - Transplant type, stem cell source, aGVHD prophylaxis
            - 4 double cord; cord blood; tacrolimus/MMF
            - 2 MSD; PBSC; 1 with tacrolimus/MTX and 1 with cyclosporine/MMF
            - 1 MUD; PBSC; tacrolimus/MTX
            - 1 mismatched (9/10 DQ) unrelated; BM; tacrolimus/MMF/RGI 2001

        - 1 cord failed haplo-identical; PBSCT → cord; tacrolimus/MMF
    - aGVHD characteristics and tocilizumab response
        - Day of onset aGVHD onset = +18 to +90
        - Overall grade of GVHD = 7 with Grade III and 2 with Grade IV
        - Organ involvement
            - 6 with GI & liver
            - 2 GI alone
            - 1 GI & skin
        - Tocilizumab
            - Day to administration from transplant = +39 to +266
            - Median time to administer from onset of aGVHD was 44 days (14-176)
            - Number of dose = median was 2 (range 1-6)
            - Days surviving since initiation
                - For the 8 patients that are deceased = 13-308
                    - Primary cause of death
                        - 5 due to aGVHD
                        - 2 due to infectious etiology (1 CMV and 1 gram-negative septic shock)
                        - 1 alveolar hemorrhage aGVHD
                - For the 1 patient alive = 759
            - Toxicity
                - Tolerable (1 patient experienced and infusion-related reaction)
                - No discontinuation due to toxicity
    - Overall response and infection rates
        - Response
            - CR = 2
            - Mixed (only 1 organ response) = 2
            - No response/progression = 5
        - Infections
            - 5 patients developed
                - 2 CMV reactivation (1 with colitis/pneumonitis → death)
                - 1 Klebsiella pneumonia → septic shock/death
                - 1 MSSA
                - 1 MRSA
- Conclusions
    - While tocilizumab may have some activity in the treatment of steroid-refractory aGVHD, it may not be significantly better than other available agents
    - A much earlier intervention (a true second-line therapy) may be beneficial
    - This report further underscores the need for better agents in aGVHD prevention and treatment

<u>Supportive Care</u>

Abstract 4591 – Impact of Prophylaxis with Defibrotide on the Occurrence of Acute GvHD in Allogeneic HSCT (Corbacioglu S, et al. *Blood.* 2013;122(21):4591)

- Background
    - aGHVD is a major complication of allo-HCT and is associated with significant morbidity and mortality (AJ Beres *J Immunol* 2012, D Weisdorf *Hematology Am Soc Hematol Educ Program* 2007, BR Blazar *Nat Rev Immunol* 2012)
    - Despite administration of prophylactic agents, incidence remains high (occurs in 35-50% of patients), thus there is a substantial unmet medical need for more effective preventative approaches (DA Jacobsohn *Orphanet J Rare Dis* 2007)

- Defibrotide has been shown *in vitro* to bind to various sites on the vascular endothelium modulating the expression status and the activity of endothelial cells (PG Richardson *Expert Opin Drug Saf* 2013, *Defitelio* product information 2013)
    - Vascular endothelium in one of the main target tissues identified in aGVHD pathogenesis (M Kummer *J Immunol* 2005), thus a potential beneficial role of defibrotide in aGHVD may be indicated
  - Benefits of defibrotide for VOD in high-risk pediatric HCT patients have been previously investigated in a phase III study (S Corbacioglu *Lancet* 2012)
- Objective
  - Analyze the effects of prophylactic administration of defibrotide on the
    - Reduction in incidence of VOD by Day +30 (primary objective)
    - Incidence and severity of aGVHD (secondary objective)
- Methods
  - Prospective, randomized, open-label controlled study conducted in pediatric patients (< 18 years old) at high-risk for hepatic VOD post-HCT
  - Standard GVHD prophylaxis was allowed according to best practice
  - Prophylaxis arm consisted of defibrotide 25 mg/kg/day IV (until hospital discharge for a minimum of 14 days) and control arm (no prophylaxis; standard of care only)
  - The authors report on the allo-HCT patients only in this investigation
- Results
  - Patients

	Defibrotide (n=122)	Control (n-117)
Median age ± SD	6.47 ± 5.28 years	6.54 ± 5.49 years
Patients < 2 years old	29%	30%
Gender (male/female)	64%/36%	58%/42%
Conditioning regimen		
Busulfan-based	62%	64%
Melphalan-based	60%	53%
Grafts from related donors	40%	30%

  - Prophylaxis with defibrotide was shown to reduce both the occurrence (p=0.0046) and severity (p=0.0034) of aGVHD significantly
  - Incidence of aGVHD at Day +100 was 47% in the defibrotide arm compared to 65% in the control arm (p=0.0046) with a consistent reduction in grade II-IV aGVHD (22% vs. 37%; p=0.0130) (grade I aGVHD was 25% vs. 28%)
  - Use of corticosteroids was significantly lower in patients receiving defibrotide prophylaxis vs. the control arm (48% vs. 68%; p=0.027)
  - Use of standard GVHD prophylactic measures were generally comparable, although a smaller number of patients in the defibrotide arm received ATG vs. the control arm (55% vs. 70%)
    - Significant effect of defibrotide were confirmed by an exploratory analysis adjusting for ATG as a covariate → adjusted risk difference for aGVHD grade II-IV for defibrotide vs. control: -0.1470; 95% CI: -0.2618, -0.0322; p=0.0121)
  - Defibrotide did not seem to affect relapse rates of leukemias by Day +100 (8% for defibrotide arm vs. 10% for control arm) or by Day +180 (10% vs. 13%)
- Conclusions
  - Defibrotide prophylaxis can reduce the incidence and severity of aGVHD in pediatric patients undergoing allo-HCT
    - Reduction is seen when defibrotide is used in combination with standard prophylaxis for GVHD
  - Significant reduction in corticosteroid use most likely reflects the lower incidence of aGVHD in the defibrotide versus control arm
  - Further studies are necessary to strengthen to preclinical (endothelial protective effect and down regulation of heparanase activity) and clinical evidence for the role of defibrotide in the prevention of aGVHD

Abstract 2057 – Inhaled Cyclosporine for the Treatment of Bronchiolitis Obliterans Following Hematopoietic Stem Cell Transplantation (HSCT) or Lung Transplantation (Gormley N, et al. *Blood.* 2013;122(21):2057)

- Background
  - Bronchiolitis obliterans syndrome (BOS)
    - Late-onset non-infectious pulmonary complications of HCT
    - Thought to be a manifestation of cGVHD
    - Mainstay of therapy is augmentation of immunosuppression
      - Limited efficacy
      - Associated with deleterious consequences (e.g., increased risk of infection, decreased GVT or GVL effects)
- Methods
  - Study investigated whether targeted, localized therapy (as inhaled cyclosporine) could improve/stabilize lung function)
  - Phase II trial of cyclosporine inhalation solution administered via nebulizer
    - 150 mg thrice weekly during Week 0
    - 300 mg thrice weekly during Week 6
  - Inclusion criteria:
    - 18-80 years
    - FEV1 <75% predicted
    - FEV1 decline > 10% compared to pre-transplant FEV1
    - No evidence of pulmonary infection as causative etiology
    - And one of the following:
      - FEV1/FEVC < 0.7
      - Air trapping seen on CT scan or RV $\geq$ 120% predicted
      - Evidence of cGVHD affecting at least one other organ system
  - Subjects characterized as having progressive or stable disease at study entry on their FEV1 values in the preceding 3-18 weeks
    - Progressive disease = $\geq$ 10% decline in FEV1
    - Stable disease = increase in FEV1 < 5% or a decrease < 10%
  - Primary endpoint = change in FEV1 at study completion (average of week 18 and 19) compared to study baseline
- Results
  - N=11 (9 evaluable for response)
    - Median age (range) = 45 years (14-73 years)
    - Gender = 5 males, 6 females
    - 9 patients underwent HCT (2 patients underwent lung transplant)
      - Conditioning
        - 4 RIC and 5 myeloablative
      - Donor
        - 5 MRD and 4 MUD
    - Median FEV1 (range) = 1.11 L (0.5-2.11 L)
    - Study baseline BOS status
      - 4 with progressive disease and 7 with stable disease
    - Median time from BOD diagnosis (range) = 9 months (2-37 months)
  - Adverse events
    - Occurred in 9 of 10 patients
    - Included cough, bronchospasm and dyspnea
    - Most were grade 2 (range of grade 1-3)
    - Occurred only during the time of inhalation
    - 3 patients went-off study (patient choice) prior to completion of the 18 weeks of the study and were considered non-responders
  - Median peak systemic absorption of cyclosporine = 99 mcg/L (range 32-263 mcg/L) 20 minutes post-inhalation

        - Lung deposition studies showed the total deposited dose averaged 12% (range 4-20%) of the inhaled dose)
    - Response
        - 4 of 8 (50%) of HCT subjected with BOS had a response, including 3 entering the study with progressive disease (1 had stable disease)
            - Among responders, improvements in absolute FEV1 from baseline were 19.5%, 15%, 12.7% and 3.4%
            - Among responders, 2 patients were able to decrease their systemic steroid therapy by 50% and 43%
            - All responders continue to receive inhaled cyclosporine on an extended access protocol
- Conclusions
    - Inhaled cyclosporine can be delivered safely to HCT patients with BOS
    - Inhaled cyclosporine resulted in minimal systemic absorption
    - Preliminary data with inhaled cyclosporine suggest efficacy of this agent for severe BOD occurring after HCT

Abstract 2986 – Evaluating Risk Factors and Outcomes for Clostridium Difficile Infection (CDI) in Stem Cell Transplant (SCT) Recipients (Shah N, et al. *Blood.* 2013;122(21):2986)

- Background
    - *Clostridium difficile* infections (CDI) are the leading cause of infectious diarrhea among patients undergoing JCT
    - Data evaluating the trends, risk factors and hospitalization outcomes in this patient population are lacking
- Objectives
    - Analyze the Nationwide Inpatient Sample (NIS) database to evaluate the trends in the incidence of CDU and the impact of CDI on hospitalization outcomes in HCT recipients
- Methods
    - Used NIS database to obtain adult data for auto-HCT and allo-HCT performed between January 2001 and December 2010
    - Separate multivariate logistic regression analyses were performed to evaluate risk factors of CDI in HCT patients and hospitalization outcomes including length of stay (LOS, in-hospital mortality (IHM) and hospitalization charges
    - Comorbidities were identified using software that created measures reported by Elixhauser et al.
- Results
    - Mean LOS (CDI vs. no CDI)
        - Auto-HCT: 26 vs. 20 days ($p < 0.0001$)
        - Allo-HCT: 42 vs. 30 days ($p < 0.001$)
    - Mean IHM
        - Auto-HCT: 4% vs. 2.2% ($p = 0.0003$)
        - Allo-HCT: 12.7% vs. 9.2% ($p = 0.0008$)
    - Mean hospitalization charges
        - Auto-HCT: $208,025 vs. $145,250 ($p < 0.0001$)
        - Allo-HCT: $367,415 vs. $270,366 ($p < 0.0001$)
    - There was an association between CDU and the presence of multiple comorbidities among auto-HCT ($p = 0.05$) and a similar trend was seen in allo-HCT patients
    - The incidence of CDI among transplant patients has remained relatively stable over time with a higher cumulative incidence among allo-HCT patients (8.29% vs. 5.63%, $p < 0.001$)
- Conclusions
    - Incidence of CDI has remained stable over time with a slightly higher risk among allo-HCT patients
    - CDI was associated with longer LOS, higher charges and higher IHM for both auto-HCT and allo-HCT patients

- While this analysis does not permit the authors to directly ascribe differences in outcome in CDI alone, the data suggest that CDI has a major morbid impact in the setting of HCT, and provides a rationale for development of more effective approaches for prevention of CDI in these patients

Abstract 4641 – Incidence and Risk Factors for Pneumocystis Jirovecii pneumonia (PCP) Following Haematopoetic Stem Cell Transplant (HSCT) (Kulkarni S, et al. *Blood.* 2013;122(21):4641)

- Background
  - Serious PCP infections are known to develop in immunocompromised individuals
    - Risks and risk factors are well established in patients with retroviral infections but parallel data is scarce in HCT patients
  - There is increasing use of newer methods to prevent GVHD (e.g., alemtuzumab) and novel conditioning regimens (e.g. RIC)
- Objectives
  - Establish the incidence and identify the risk factors for PCP infections in HCT patients
- Methods
  - Analysis of 1129 patients undergoing 1184 HCT procedures between 2002 and 2012
- Results

Patient Characteristics	Autograft (n=818)	Allograft (n=368)
Median age, years	55 (15-73)	46 (16-71)
Gender, male	65%	66%
Diagnosis		
Acute leukemia	36	207
Myeloma	15	464
Lymphoma	329	70
Other	35	45
Risk category		
Good	74%	76%
Poor	26%	24%

HCT Characteristics	Myeloablative (n=157)	RIC (n=211)
Median age, years	37 years (17-64)	55 years (17-71)
Donor		
Sibling	84	78
MUD	73	133
Conditioning		
TBI/No TBI	140/17	27/184
Campath	24	143
ATG	1	23
Stem cell source		
PBSC	116	184
BM	40	26
PBSC + BM	0	1
UCB	1	0

  - PCP developed in 7 autograft and 24 allograft patients
  - Median time to development of PCP was 13 months and 10 months in auto- and allograft patients, respectively
    - 58% of infections developed after Day +180
  - Overall risk of developing PCP at one year was 0.2% in autograft patients and 8% in allograft patients
    - Most common manifestations of infection were chest symptoms (84%), x-ray changes (95%) and CT changes (64%)
    - Only 13% of patients had co-infection with another pathogen

- There was no effect of age at the time of transplant, gender or disease risk status on the risk of developing PCP
- Risk identified for development of PCP
  - Type of donor: MUD > MSD > Auto-HCT ($p < 0.0001$)
  - Use of Campath/ATG ($p < 0.0001$)
  - Type of conditioning: RIC > Myeloablative, Auto-HCT ($p < 0.0001$)
  - PCP prophylaxis: Azithromycin > Pentamidine, None, Co-trimoxazole ($p=0.006$)
  - Multivariate analysis
    - Auto-HCT
      - No-Septrin prophylaxis
        - HR 1.74 (95% CI: 0.9-3.0; $p=0.073$)
    - Allo-HCT
      - RIC conditioning
        - HR 5.24 (95% CI:1.2-22.1; $p=0.028$)
      - No-Septrin prophylaxis
        - HR 1.67 (95% CI:1.1-2.5; $p=0.013$)

- Conclusions
  - Risk of PCP infection is high in patients receiving Campath/ATG for RIC allo-HCT
    - Due to retrospective nature of this study, effect of RIC conditioning form the use of Campath could not be differentiated
  - Most infections developed beyond 6 months and prophylaxis for 12 months is needed
  - Non-Septrin containing prophylactic measures are ineffective, especially the use of single-agent azithromycin
  - Due to small sample size, it was not possible to identify the role played by lymphocytes, GVHD therapies and events after relapse of the underlying malignancy

Abstract 4631 – Palifermin for Prevention of Oral Mucositis Has No Negative Effect on Long-Term Outcome in Patients with Hematological Malignancies Undergoing HSCT - Long-Term Follow-Up (Stiff P, et al. *Blood.* 2013;122(21):4631)

- Background
  - Palifermin had been shown to reduce the incidence and duration of severe oral mucositis in HCT patients (B Nasilowska-Adamska *Bone Marrow Transplant* 2007)
    - Acts physiologically on epithelial cells that express the keratinocyte growth factor (KGF) receptor, stimulating their proliferation, differentiation and survival
  - Hematologic tumor cells do not express the KGF receptor, so it is unlikely that the administration of pharmacologic doses of palifermin for the prevention/treatment of oral mucositis in patients with hematologic malignancies would have a direct effect on the existing primary tumor
    - Survival and incidence of secondary malignancies of epithelial cell origin could be affected
- Objectives
  - Compare long-term disease outcome (OS, disease progression and incidence of secondary malignancies) in patients with hematologic cancers undergoing HCT in those receiving palifermin to prevent oral mucositis vs. placebo
  - Detail any potential late complications due to palifermin exposure
- Methods
  - Eligible patients were those with hematologic malignancies undergoing high-dose cytotoxic therapy with auto-HCT initially enrolled in 4 studies conducted at 31 sites in the US, Europe and Australia between 1997 and 2005 (S Durrant *Blood* 1999 (abstract 3130), R Spielberger *Proc ASCO* 2001 (abstract 25), R Spielberger *New Engl J Med* 2004, Sobi-Data on file)
    - Had to have completed or withdrew from 1 of 4 studies and received at least 1 dose of palifermin regardless of treatment assignment
  - The data cutoff was October 2012 for which 177 patients were still active in the study
- Results
  - Patient disposition

        - 672 patients enrolled on 4 studies → 662 patients included in the survival analysis → 543 patients in the follow-up study (345 received palifermin)
    - Median follow-up time was 7.9 years (0.1-14.9 years) for the palifermin group and 8.8 years (0.1-14.8 years) for the placebo group
    - Palifermin
        - Dose exposure range: 5-80 microgram/kg
        - Dose level
            - 14% < 60 microgram/kg
            - 68% 60 microgram/kg
            - 18% > 60 microgram/kg
        - Number of doses: 3-6
    - Survival times
        - No significant difference was observed between treatments in OS or PFS
    - Secondary malignancies
        - No significant difference in the incidence of secondary malignancies was reported between patients receiving palifermin and placebo
- Conclusions
    - OS, PFS and incidence of secondary malignancies were comparable with palifermin and placebo in patients undergoing HCT
    - After a follow-up time of up to 15 years (corresponding to 3557 patient years), no negative effect of palifermin on long-term outcome was observed

Appendix II – Select Education Sessions
2013 American Society of Hematology (ASH) Annual Meeting Updates
Susannah E. Koontz, Pharm.D., BCOP
February 14, 2014

NOTE: Information contained in this supplemental handout is provided to you for your reference only. It is not endorsed by the Programming Committee of the ASBMT Pharmacy SIG or by the Accreditation Council for Pharmacy Education (ACPE). While every effort has been made to ensure accuracy at the time of compilation, please refer to original publication material(s) to confirm information.

Special Education Session – Chimeric Antigen Receptors (CARs): Driving Immunotherapy – Stephen Grupp, MD, PhD and Elizabeth J. Shpall, MD

- Roadblocks to successful cellular immunotherapy for cancer
    - Problems → solutions
        - Targeting → CAR or TCR
        - Expansion *ex vivo* → GMP cell culture
        - Proliferation in the host → ? Young T-cells
        - Persistence → ? Memory T-cells
        - Effector:Target ratio --? Create sufficient effector cells for clinical success
            - Ideally there would be an efficacy signal, not just safety In phase I
- *Ex vivo* approaches for adoptive T-cell therapy
    - Antigen-specific stimulation
    - Polyclonal stimulation
- Evolution of CARs with additional costimulatory domains – see Sadelain *Cancer Discov* 2013
- Redirecting the specificity of T-cells
    - Gene transfer technology is used to stably express CARs on T-cells, conferring novel antigen specificity
    - Transduction
        - Many retroviral
        - Some now using lentiviral
        - Non-viral Sleeping Beauty system
    - Temporary modification with RNA transfection
    - Suicide systems
- Cell therapy challenge
    - Cells having drug-like kinetics – number of cells degrade over time (see JN Kochenderfer in *Blood* 2010 and *Blood* 2012)
    - Modified T-cells detectable at high levels by flow cytometry with longer persistence (as shown by SA Grupp in *New Engl J Med* 2013)
- Properties of anti-CD3/CD28 costimulated expansion system
    - Clinical scale up – no feeder cells required
    - Expansion > 10^6-fold
    - Repertoire preserved
    - T-cells persist after infusion
    - Maintains function and homing of T-cells
    - Induction of telomerase – minimize replicative senescence
    - Refs: BL Levine *J Immunol* 1997, RG Carroll *Science* 1997, NP Weng *Immunol Rev* 1997, LM Humeau)
- Outstanding issues with CAR therapy
    - Persistence (correlates with outcome)
        - Vector

        - SCFV or endodomain construction
        - Bulk of disease
        - Pre-Infusion therapy
        - Post-infusion therapy
        - Cell type modified
        - Disease targeted
        - Manufacturing
    - *Ex vivo* expansion
        - CD3x28 beads
        - OKT3/IL-2
        - Antigen presenting cells
        - Cytokines
        - Duration of *ex vivo* culture
    - Pre-infusion therapy (lymphopenia? Treg decrease?)
        - No therapy
        - Lymphodepleting chemotherapy
        - Stem cell transplant
    - Homing
        - CNS
            - Need to consider issues with neurotoxicity
                - Seen in several CD19 trials (NCI, CHOP/UPenn, blinatumomab)
                - Self-limited, generally untreated, fully resolves
                - ??? Related to cytokine release syndrome
                - Not prevented by tocilizumab
        - Other sanctuary sites
    - On target toxicity
        - B-cell aplasia
        - Cytokine syndrome
            - May be significant, but highly variable across patients and studies
            - May or may not scale with dose, but may scale with disease burden
            - ??? Different with across diseases
            - Different in the era of highly reactive CAR cell therapy
            - IL-6 is an important driver of toxicity
            - Entirely reversible with cytokine blockade
                - IL-6R blocking agent tocilizumab (Actemra®)
                    - Indicated in juvenile idiopathic arthritis (JIA), rheumatoid arthritis (RA), and in Japan for Castleman's Disease
                    - Typically given monthly
                    - Rare side effects if transaminitis and neutropenia
                    - Dose of 8 mg/kg has been used in patients receiving CAR therapy (see SA Grupp *N Engl J Med* 2013)
        - Macrophage activation syndrome (MAS)/Hemophagocytic lymphohistiocytosis (HLH)
            - Extraordinarily high ferritin levels after highly active CAR infusions suggest MAS/HLH
                - In the studies performed by University of Pennsylvania: 16,000-415,000 ng/dL
            - Coagulopathy
                - Elevated D-dimer and low fibrinogen
            - Liver: HSM and transaminitis
            - Moderate marrow hematophagocytosis
            - Entirely reversible with cytokine blockage

        - Blinatumomab causes MAS/HLH as well and is reversible with tocilizumab (see DT Teachey *Blood* 2013
    - What cells should be CAR-modified?
        - Cord blood vs. peripheral blood
        - T-cells
        - NK cells
        - iNKT cells
        - ES/IPS cells
    - What tumors should be targeted?
        - ALL, CLL, NHL
        - Multiple myeloma
        - Solid tumors
- Examples of CARs currently under development
    - B-cell leukemia/lymphoma: CD19, CD20, CD22, CD30
    - Ovarian carcinoma alpha-folate receptor
    - Renal cell carcinoma: CAIX
    - Colon carcinoma: CEA, Lewis-Y
    - Breast carcinoma: Her2
    - Melanoma: GD3
    - Neuroblastoma: GD2
- Highlights of clinical data being presented at the 2013 ASH Annual Meeting
    - Abstract 152 by Cruz et al
        - Disease: post allo-B cell tumors
        - Target: CD19
        - Subjects: 9
        - Vector: Retro/Trivirus
        - Signaling endodomains: CD28 and CD3zeta
        - Pre-T-cell prep: none
        - Persistence: 8-9 weeks
        - Key take-home points
            - Trivirus approach to maintain persistence
            - Potential antiviral activity
            - 2 responses with decrease/clearing of peripheral blood disease, 2 CRs pre-cell therapy maintained
    - Abstract 69 by Davila et al
        - Disease: ALL
        - Target: CD19
        - Subjects: 13 adults
        - Vector: Retro
        - Cell manufacturing: CD3/28 beads
        - Signaling endodomains: CD28 and CD3zeta
        - Pre-T-cell prep: lymphodepleting chemotherapy
        - Persistence: going to HCT
        - Key take-home points
            - 10/12 patients with measurable disease became MRD-negative
            - Bridge to HCT
            - Rapid responses
    - Abstract 67 by Grupp et al
        - Disease: ALL
        - Target: CD19
        - Subjects: 16 children and 4 adults
        - Vector: Lenti

        - Cell manufacturing: CD3/28 beads
        - Signaling endodomains: 4-1BB and CD3zeta
        - Pre-T-cell prep: lymphodepleting chemotherapy in most, but not all, patients
        - Proliferation: high
        - Persistence: 1-15 months
        - Key take-home points
            - Significant proliferation
            - Persistence in some but not all
            - Many treated post-allo-HCT with not GVHD
            - Response in refractory disease possible without lymphodepleting chemotherapy
    - Abstract 163 by Kalos et al
        - Disease: ALL/CLL
        - Target: CD19
        - Subjects: 38 adults/children
        - Vector: Lenti
        - Cell manufacturing: CD3/28 beads
        - Signaling endodomains: 4-1BB and CD3zeta
        - Pre-T-cell prep: lymphodepleting chemotherapy in most, but not all, patients
        - Proliferation: high
        - Persistence: 1-36 months
        - Key take-home points
            - Significant proliferation (and proliferation associated with response)
            - Deep sequencing MRD (adaptive) to show deep molecular response
            - High IL-6 associated with cytokine release syndrome/macrophage activation syndrome
    - Abstract 166 by Kebriaei et al
        - Disease: NHL/ALL
        - Target: CD19
        - Subjects: 13 adults
        - Vector: Sleeping Beauty
        - Cell manufacturing: APC-OKT3, IL-2, IL-21
        - Signaling endodomains: 4-1BB and CD3zeta
        - Pre-T-cell prep: HCT
        - Key take-home points
            - Safe
            - Treatment in post-HCT MRD setting
            - No post-auto-HCT relapses in lymphoma with persistence documented
    - Abstract 168 by Kochenderfer et al
        - Disease: NHL
        - Target: CD19
        - Subjects: 14 adults
        - Vector: Retro
        - Cell manufacturing: rapid 10 day culture
        - Signaling endodomains: 4-1BB and CD3zeta
        - Pre-T-cell prep: lymphodepleting chemotherapy with fludarabine/cyclophosphamide
        - Proliferation: high
        - Persistence: up to 3 months B-cell aplasia
        - Key take-home points
            - 79% RR, 5/13 CRs
            - Major response including DLBCL
            - Evolving responses

- Abstract 163 by Kalos et al
  - Disease: ALL/CLL
  - Target: CD19
  - Subjects: 38 adults/children
  - Vector: Lenti
  - Cell manufacturing: CD3/28 beads
  - Signaling endodomains: 4-1BB and CD3zeta
  - Pre-T-cell prep: lymphodepleting chemotherapy in most, but not all, patients
  - Proliferation: high
  - Persistence: 1-36 months
  - Key take-home points
    - Significant proliferation (and proliferation associated with response)
    - Deep sequencing MRD (adaptive) to show deep molecular response
    - High IL-6 associated with CRS/macrophage activation syndrome
- Abstract 68 by Lee et al
  - Disease: ALL (1 NHL)
  - Target: CD19
  - Subjects: 8 children
  - Vector: Retro
  - Cell manufacturing: bead stimulated 11 day culture, fresh infusion
  - Signaling endodomains: 4-1BB and CD3zeta
  - Pre-T-cell prep: lymphodepleting chemotherapy fludarabine/cyclophosphamide
  - Proliferation: high
  - Persistence: mean of 55 days
  - Key take-home points
    - 63% CR rate
    - Some post-all-HCT without GVHD
    - 4/5 CRs had hematogones by Day 28
- Abstract 873 by Porter et al
  - Disease: CLL
  - Target: CD19
  - Subjects: 27 (with 10 treated at the time of abstract submission Summer 2013)
  - Vector: Lenti
  - Cell manufacturing: CD3/28 beads
  - Dose optimization study: T-cell dose of 5×10^7/kg vs. 5×10^8/kg
  - Signaling endodomains: 4-1BB and CD3zeta
  - Pre-T-cell prep: lymphodepleting chemotherapy
  - Proliferation: high
  - Persistence: (see Kalos abstract #163)
  - Key take-home points
    - No significant impact of dose on toxicity or efficacy apparent at present
- Abstract 506 by Ramos et al
  - Disease: NHL/CLL/MM
  - Target: kappa light chain
  - Subjects: 10 adults
  - Vector: Retro
  - Cell manufacturing: varied – some OKT3 and some CD3/CD28
  - Signaling endodomains: CD28 and CD3zeta
  - Pre-T-cell prep: lymphodepleting chemotherapy cyclophosphamide
  - Persistence: 1.5-9 months
  - Key take-home points

        - Novel target that may be sparing of normal lambda+ B-cells (thus less B-cell aplasia
        - Novel disease (MM)
- What is the potential for immunotherapy?
    - Consolidate patients with MRD
    - Re-induce remission
    - Produce MRD-negative status prior to allo-HCT
    - Serve as a bridge to HCT
    - Multicenter trials in pediatric ALL
    - ***With adequate persistence, can we imagine a replacement for HCT?***
- To read the personal story of the first pediatric patient, Emily "Emma" Whitehead, to be treated with CTL019 (as reported in the *New England Journal of Medicine* by SA Grupp, et al in 2013), please visit:
    - The Children's Hospital of Philadelphia website
        - http://www.chop.edu/service/oncology/patient-stories-cancer/leukemia-story-emily.html
    - The patient's personal website/blog
        - http://emilywhitehead.com/

Allogeneic Transplant for High Risk Myelodysplastic Syndromes and Acute Myeloid Leukemias: Are We Improving Outcomes?

Allogeneic Transplantation for AML: GVL versus GVHD and Disease Recurrence – Koen van Besien

- Trends in allo-HCT by recipient age
    - In 1990's less than 10% of patients over 50
    - Today, 30% > 50 years
    - Not uncommon to do transplants in 60's and 70's
        - Patient older, MSD older → so they are often transplanted with MUD's
- Example – 60 year old male with AML CR1
    - No HLA-sib, had ~30 MUDs and about 10 cord blood donors
- How to fine tune the donor search?
    - Unrelated donor selection
        - Donor gender and parity
        - Donor age is adverse in URD (see Finke in *Biol Blood Marrow Transplant* 2012)
        - Donor/recipient CMV status impact on survival particularly in ALL (see Schmidt Hieber *Blood* 2013)
            - But CMV reactivation may decrease recurrence rate
        - Donor blood group
        - High resolution HLA, B, C and DR donor matching
            - Allele matching at these loci is important for outcome!
            - 1 antigen mismatch reduces survival by 10% and has a cumulative effect with number of mismatches
        - HLA DP and other low expression HLA antigens
            - Lack of linkage disequilibrium of HLA DP with other HLA's is such that DP matching occurs by chance in only 25% of 8/8 D/R pairs
            - Initial studies showed minimal impact of DPB1 mismatching on long-term outcome
                - Petersdorf *Blood* 2000: double mismatch increases aGVHD
                - Shaw *Leukemia* 2010: DPB1 matching improves outcome in early, but not late stage disease
                    - In mismatch HCT, DP mismatching is beneficial
            - Permissive mismatches with DPB1

        - DPB1 0901 in donor is immunogenic and target for rejection (Fleishauer *Blood* 2001)
        - Some DPB1 mismatches are tolerated (permissive) and others are not (Zino *Blood* 2004)
        - A DP permissive mismatch occurs by chance in 50% of D/R pairs
        - Non permissive DPB1 disparity is a significant risk factor for mortality after URD HCT (Crocchiolo *Blood* 2009, *Lancet Oncol* 2012)
        - Conclusion
            - Non-permissive DP mismatching occurs by chance in 25% of otherwise A, B, C, DR matched D/R pairs
            - It is associated with increased TRM and decreased survival
            - Perfect DP matching may be achievable for only a minority of patients
            - Permissive DP mismatching may be achievable by using straightforward algorithms in the majority of patients
            - Use of this strategy should reduce TRM and improve survival
            - Multiple mismatching for DPA1, DQA1, DQB1 or DR53/54 may have an impact in 7/8 URD (Fernandez-Vina *Blood* 2013)
    - KIR typing
        - Several models exist for the relation between KIR genotype/function and transplant
            - Missing ligand (mostly halp-HCT)
            - Activating genotype
        - Models are not entirely consistent with one another
        - Though KIR genotype clearly relates to transplant outcome, refinement of models is necessary
            - See abstracts 549 and 731 at the 2013 ASH meeting
- What about GVHD prophylaxis in AML?
    - Is cGVHD good or bad?
        - None → more relapse but some cGVHD was good (see Horowitz *Blood* 1990 – patients were young and many had CML, which is sensitive to GVL)
        - Baron *J Clin Oncol* 2005 – GVT effects after allo-HCT with non-myeloablative conditioning
            - Grade II-IV aGVHD had no significant impact on the risk of relapse or progression but was associated with increased risk of NRM and decreased probability of PFS
            - Extensive cGVHD was associated with decreased risk of relapse/progression and increased probability of PFS
            - Follow-up paper in *J Clin Oncol* 2013 from the same group in Seattle
                - Potential benefit associated with cGVHD was outweighed by increased NRM
                - Much older patients in this paper
        - All-cause mortality in 1479 2-year survivors after allo HCT (Bhatia *Blood* 2007)
            - In AML
                - No GVHD 10-year = 92%
                - GVHD 10-year = 73%
                - RR NRM = 3.4
                - RR relapse rate mortality = 1.8 (hard to manage late-relapse disease)
        - Summary
            - Virtually all studies indicate a detrimental effect on cGVHD on survival
                - See Weisdorf *BBMT* 2012 and Baron *Leukemia* 2012
            - Detrimental effect becomes more apparent with prolonged follow-up

- Causes of late death are varied and include infections, cardiac complications, pulmonary complications, but also difficulties in managing late recurrences
- Reduction in rates of recurrence rate is far outweighed by excess morbidity and mortality
- Better prevention of cGHVD will improve morbidity associated with HCT
- It will also improve survival and acceptability of transplant

- Standard GVHD prophylaxis
  - See Anasetti *New Engl J Med* 2012 for the CNI + MTX study
  - What about *in vitro* T-cell depletion
    - Negative selection: complement and monoclonal antibodies, T10B9
    - Positive selection: elutriation, CD34 selection
    - See Ho *Blood* 2001
      - Advantages
        - Low incidence of aGVHD and cGVHD
        - Reduced or no requirement for post-HCT immunosuppression
        - Decreased pulmonary and hepatic toxicity
        - Decreased early TRM
        - ? shorter time to engraftment
        - ? decreased costs
      - Disadvantages
        - Higher incidence of graft failure
        - Higher incidence of disease relapse (especially with CML)
        - Delayed immune reconstitution
        - Increased risk for EBV-PTLD
        - Higher incidence of CMV reactivation
        - OS not improved
    - Additional studies by Wagner 2005, Pasquini 2012 and Bayraktar 2013
    - For AML, this is a reasonable approach and probably superior to standard GVHD prophylaxis
  - What about *in vivo* T-cell depletion
    - 4 agents (see ASH Education Book for comparative studies chart)
      - ATGAM (horse)
      - Thymoglobulin (rabbit)
      - ATG-Fresenius (rabbit)
      - Alemtuzumab (monoclonal antibody)
    - Summary
      - *In vivo* T-cell depletion with ATG or alemtuzumab is reasonable and probably superior to standard GVHD prophylaxis
      - It reduces aGVHD and CGVHD with minimal impact on relapse rates
      - In experienced centers, infectious complications (ATG and alemtuzumab) and PTLD (ATG) can be minimized
      - Horse ATG is likely more toxic in this setting
      - Routine use of rabbit ATG in URD is supported by European consensus recommendations (Ruutu *BMT* Epub)
  - Other
    - Post-HCT MMF – see abstract 731 at 2013 ASH meeting
    - Post-HCT CTX – see abstract 3310 at 2013 ASH meeting

- Cord blood in AML
  - See Abstracts 302 and 3339 at 2013 ASH meeting
  - See Eapen *Lancet* 2007 for selection criteria
    - Matching criteria by Eapen in *Blood* 2013 as well as abstract 414 at 2013 ASH meeting

Pharmacologic Methods to Reduce Disease Recurrence – Charles Craddock

- Introduction
  - Allo-HCT now plays a central role in the management of HR-AML and MDS due to the advent of reduced intensity conditioning regimens and increased donor availability
  - Decision to proceed to transplant by a dynamic assessment of:
    - Predicted relapse risk if the patient is treated with chemotherapy alone
    - Estimated TRM based on donor (HLA disparity) and the patient (co-morbidities)
  - Opportunity to safely deploy a GVL effect has dramatically extended curative options to AML and MDS patients
- Potent GVL effect is exerted after a myeloablative allograft for AML (see Bacigalupo *Blood* 1991
- Relapse is the major cause of treatment failure in patients allografted for AML and MDS
  - Disease relapse occurs in 20-75% of patients post-allograft and now represents the major cause of treatment failure
  - Outcome in patients with AML who relapse after allo-HCT is extremely poor
  - Rational deployment of novel strategies to prevent relapse will be dependent on accurate risk stratification and advances in our understanding of tumor biology
  - For outcome data in AML after relapse post-HCT, see C Schmid *Blood* 2012
  - Disease burden is an important predictor of relapse risk in allografted AML patients
    - See C Craddock *Haematologica* 2010 for impact of disease stage
    - See Walter *J Clin Oncol* 2011 for impact of MRD status
  - Disease biology is a major determinant of disease relapse after allo-HCT for AML
    - See Chevalller *Bone Marrow Transplant* 2012 for importance of karyotype
    - See Brunet *J Clin Oncol* 2012 for importance of FLT3-ITD status
  - Conditioning regimen intensity determines relapse risk post allo-HCT (see Lioure *Blood* 2012)
    - OS was similar between MAC and RIC
    - Relapse and NRM higher with RIC compared to MAC
    - See Blaise *Cancer* 2013 → not all RIC are the same!
  - Are leukemic stem cells a reservoir of relapse post-HCT?
    - Do leukemic stem cells disappear in patients who are eventually cured and persist in those that relapse?
      - See Van Rhenen *Blood* 2007, Gerber *Blood* 2012, Craddock *Leukemia* 2013
    - Pre-transplant leukemia stem cell is an independent predictor of outcome (see Bradbury form the 2012 ASH Annual Meeting)
- Pharmacologic opportunities to optimize leukemia stem cell targeting in patients allografted for AML/MDS
  - Minimize pre-transplant disease burden
    - No impact of post-remission chemotherapy on outcome after a myeloablative allograft (Tallman 2000)
    - No evidence of benefit of cytarabine consolidation prior to a RIC allograft (Warlick 2013)
    - Prospective studies correlating impact of pre-transplant cytoreduction on MRD and outcome required
  - Optimize cytotoxic properties of the conditioning regimen
    - Excessive toxicity of MAC regimens in older patients provided the rationale for the development of RIC regimens
    - Advent of new cytotoxic drugs and improved supportive care has increasingly uncoupled myeloablation from transplant toxicity rendering the MAC/RIC distinction less irrelevant
    - In principle there are now no *a priori* reasons why increased age is a contraindication to the delivery of a MAC
    - Retrospective analyses have focused on the MAC/RIC dichotomy: what is now required are disease specific comparisons between individual transplant regimens with the emphasis on the key outcomes of toxicity and relapse

        - See Copelan *Blood* 2013 for IV Bu/Cy improving OS and reducing relapse risk in patients allografted for AML
        - Development of novel conditioning regimens in AML/MDS
            - Andersson 2002: Flu/IVBu – modest toxicity with low relapse rate (randomized comparison with IVBu/Cy awaiting
            - Nemecek 2011: treosulfan – encouraging phase II data combined with Flu (see Nagle abstract 545 from 2013 ASH meeting)
            - Andersson 2011: clofarabine (see also abstract 413 by Chevallier at 2013 ASH meeting)
    - Target leukemia specific antigens post-HCT
        - Adjunctive biological therapies with direct anti-tumor effect
            - Abstract 143 at 2013 ASH meeting by Gill et al
            - Olavarria 2007: imatinib for CML (eliminating need for DLI)
                - Post-HCT TKIs have the capacity to either directly augment anti-tumor activity or delay the requirement for DLT thereby dissociating GVHD and GVL
            - Cortes (abstract 494 at 2013 ASH meeting): quizartinib in FLT3-ITD+ AML
            - Pollard (abstract 3969 at 2013 ASH meeting): sorafenib in pediatric patients with FLT3-ITD+ AML
            - What about azacytidine
                - Work done by M de Lima (2008)
            - Lenalidomide
                - See Sockel 2012
        - Optimizing a GVL effect
            - Tailored GVHD prophylaxis regimens
            - Early utilization of DLI
            - See Craddock in *Haematologica* 2010
    - Optimizing GVHD prophylaxis and post-HCT immunosuppression
        - Post-HCT immunosuppression is a critical, regimen-dependent determination of relapse
            - Optimal duration and intensity of post-HCT immunosuppression in T-replete and T-deplete allografts yet to be determine
            - See abstract 2097 by Stefanski at 2013 ASH meeting for information on higher cyclosporine levels after UCB for acute leukemia resulting in improved survival
        - Novel GVHD prophylaxis regimens may augment immune reconstitution or simultaneously target residual tumor cells
            - Armand 2008: effective incorporation of the mTOR inhibitor rapamycin into GHD prophylaxis
            - Koreth (2013): peri-transplant bortezomib
- Conclusions
    - Correlative studies to characterize the cellular reservoir of resistant disease in patients who relapse post-HCT are required
    - Advances in busulfan delivery have improved outcome by reducing transplant toxicity and relapse
    - There is an urgent requirement for novel conditioning regimens with the ability to reduce relapse without increasing toxicity
    - Combining RIC allografts with adjunctive targeted therapies may decreased relapse and dissociate GVHD and GVL
    - Our current knowledge deficit in this are mandates enrollment into clinical trials where possible

Older Patients/Older Donors: Choosing Wisely – Andrew S. Artz

- The transplant triad specific to older patients
    - Disease

        - Higher disease prevalence
        - More resistant disease
        - Disease often associated with adverse features
    - Donor
        - Older sibling donors
        - Limited data for alternative donors
    - Patient
        - Impaired tolerance to HCT
        - Long-term benefits – is it worth it?
- The patients > 60 years old is a fast growing group in which we are transplanted
    - See BL McClune *J Clin Oncol* 2010 for data in patients with AML/MDS after RIC/NMA in patients > 40 years old
        - Recipient age doesn't limit the ability to mount a GVL effect
- Health status to determine HCT eligibility in 2013
    - Age for exclusion, conditioning approach
    - PS for exclusion
    - Comorbidity is an emerging tool – how best to use this?
        - See M Sorror *JAMA* 2011 for HCT-Comorbidity Index (HCT-CI)
            - Helps to stratify patients
            - But patients with comorbidities may benefit the most with HCT
            - Can't really use this alone
        - See *JAMA* 2013 for Predicting 10-year mortality for older adults ("staging the age")
        - See Artz *Biol Blood Marrow Transplant* 2006 (retrospective)
            - Combining comorbidity and PS to estimate HCT TRM
        - See L Muffly *Biol Blood Marrow Transplant* 2013 (prospective)
            - High prevalence of vulnerabilities prior to HCT in patients 50+ years old
    - Geriatric assessment items
        - Activity of daily living
- Donor age
    - G-CSF mobilization: modest effect on older age (Vasu in *Blood* 2008, E Richa *Biol Blood Marrow Transplant* 2009)
    - Improved OS with older MSD vs. MUD as per the CIBMTR analysis (See A Alousi *Blood* 2013)
    - Similar outcomes in AML for MSD vs. MUD for AML CR1 60-74 years by S Devine on behalf of the CALGB 100103/BMT CTN 0502 group as presented at the 2012 ASH meeting
    - MDS – conflicting data
        - Kroger *Leukemia* 2013
            - Younger unrelated donors tended to do better
        - Saber *Blood* 2013
- Conclusions
    - Reasonable outcomes for hematologic malignancy after allo-HCT
    - Comorbidity and function can predict survival
    - Should not exclude older matched sibling donors
    - Early referral and HLA typing is critical for older patients with good PS

A Fresh Look at Drug Approval: Moving Away from Tradition

Drug Discovery in Rare Indications: Opportunities and Challenges – Victoria M. Richon

- Rare diseases and orphan drugs
    - Rare disease = one affecting fewer than 200,000 people in the US
        - There are 6,000-8,000 rare diseases
        - 70-75% have a prevalence of < 100,000 people

    - Orphan drug = one that has been developed to treat a rare disease
        - More than 2,200 molecules designated as orphan drugs
        - More than 400 approved since 1983 (when Orphan Drug Act initiated)
    - Refs: O Wellman-Labadie *Health Policy* 2010, E Tambuyzer *Nat Rev Drug Discov* 2010
- Orphan drug approval classified by therapeutic indication – see 2013 ASH Education Book for pie chart
    - Oncology is the most common (27%) followed by other (26%) and endocrine/metabolic (15%)
- See 2013 ASH Education Book for examples of oncology orphan drug designations and approvals between 2010 and 2013 (also on the FDA website)
- Drug discovery in rare diseases: from the bed to the bench and back again
    - Disease subset understanding → preclinical models reflecting disease subsets → identification of selective inhibitors → clinical trials in identified patient subsets → disease subset understanding
- Example of a disease subset is 11q23 leukemia subset (AT Look *Science* 1996)
    - MLL and alterations in leukemia (Hess in *Mol Med* 2004 for background information)
- DOT1L-mediated histone H3K79 methylation in MLL-rearranged leukemia (see Kristov *Nat Rev Cancer* 2007, Kristov *Cancer Cell* 2008, Allis *Nat Rev Cancer* 2010)
    - Nice model system for drug development (hypothesis in Sept 2008 to filing of IND in June 2012)
    - Have nice markers to look at efficacy
    - Can easily identify patients with aberration
    - Development of selective DOT1L inhibitors
        - EPZ004777 (Daigle *Cancer Cell* 2011)
        - Daigle *Blood* 2013 is the proof of concept
    - Clinical trials started Sept 2012 by Epizyme (EPZ-5676)
    - Summary of DOT1L inhibitors
        - Potently block enzyme activity
        - Selectively decreases methylation of H3K79 in cells
        - Reverse MLL-driven gene expression
        - Selectively kill MLL-rearranged leukemia cells
        - Efficacious in MLL-rearranged leukemia xenograft models
        - In clinical trial evaluation in patients with MLL-rearranged leukemia
        - Received orphan drug status
- Summary
    - Opportunities
        - Increased understanding of cancer subtypes provides opportunities for focused drug discovery and development
        - Ability to conduct smaller studies in selected patients
    - Challenges
        - Lack of predictive preclinical models reflecting cancer subtypes
        - Development of biomarker assays for patient selection
        - Ability to identify and recruit patients

Accelerating Safe Drug Development: An Ideal Approach to Approval – Michael R. Grever

- Developing anti-cancer agents introduction – want to accelerate without compromising safety!
    - Identify and optimize novel strategically important molecules for targeting cancer (can easily take 1-2 years)
    - Characterize biologic effects with assays for pharmacodynamics and pharmacogenomics while incorporating real-time pharmacokinetics (need to validate assays – what patients are optimal to use in?)
    - Complete early phase I/II studies and follow through with expanded phase III clinical trials when appropriate
    - Teamwork and accountability for task completion (and do it on time)
- Targeted cancer drug development
    - Higher response rate than cytotoxic agents

    - Specificity may afford improved therapeutic index
    - Drug resistance may circumvent target inhibition
    - Define kinetics of target inhibition and recovery
    - Identification of effective agent does not preclude exploration of additional novel agents
    - Strategic combination must be aggressively pursued
    - Pharmaceutical sponsors must be engaged
    - Efficient protocol design and implementation must be accompanied by robust patient accrual
    - Multiple institutions collaborate to efficiently identify patients based on molecular or genomic eligibility criteria
    - Inter-institutional monitoring to guarantee safety of early clinical trials
- Preclinical and clinical drug development pipeline
    - Need to consider doing some stages in parallel rather than in series to be more efficient in the process
    - Bring the physician scientist into the process as early as possible
    - Teamwork – testing hypotheses and not just the drugs!
- Early phase clinical trials in cancer
    - Explore optimal dose, schedule and route of administration
    - Define dose-related toxicities
    - Characterize pharmacokinetics and pharmacodynamics
    - Identify metabolites and kinetics of elimination
    - Explore biomarkers to predict response and toxicities
    - Establish phase II dose and schedule for further evaluation
    - Plan subsequent phase II studies, either alone or in strategic combinations
- Phase I study design and execution
    - Careful review of all preclinical data
    - Construct a strong scientific hypothesis
    - Enrichment population for specific target (e.g., BRAF inhibitors)
    - Prospective sequencing for molecular enrichment
    - Retrospective sequencing for exceptional responders
    - Biopsy before, during and after treatment to determine target inhibition and potential mechanisms of resistance
    - Dose escalation strategy
        - Cohorts of 3 (3 x 3 traditional)
        - Accelerated dose escalation (PK-guided: fewer patients treated at ineffective doses)
- Examples discussed during the session: pentostatin, ibrutinib, paclitaxel
- FDA regulatory requirement
    - Drugs must be safe and provide substantial evidence of effectiveness from adequate and well-controlled clinical investigation
    - In 1992, new regulations adopted for accelerated approval of agents for serious and life-threatening diseases that show improvement over available therapy
    - After gaining accelerated approval based on surrogate end point, sponsor must complete phase IV post-marketing commitment to prove clinical benefit
- Drug safety, evaluation and access
    - Before approval, all serious toxicities must be promptly reported to sponsor and the FDA
    - Following drug approval, mandatory reporting of toxicity by sponsor and voluntary report by health care provide to FDA (MEDWatch Program)
    - FDA usually requires two studies for drug approval
    - FDA provides mechanism for access to investigational agents for serious, life-threatening diseases through expanded access programs
- FDA's expedited programs/novel approaches to drug approval: serious conditions
    - Fast Track: data potential to address unmet medical need; opportunities for frequent interaction

- Breakthrough Therapy: clinical evidence indicates substantial improvement over available therapy; extensive guidance on efficient drug development program
- Accelerated Approval: meaningful advantage over available therapies with effect on surrogate or clinical endpoints
- Priority Review: provides significant improvement in safety or efficacy; shorter review (e.g., 6 months)

Phase 4 Research – What Happens When the Rubber Hits the Road? – Mark Crowther

- Traditional drug development
  - Well established process that is mimicked roughly around the world
  - New drug application (NDA) – drug sponsors approach FDA to approve a new pharmaceutical for sale and marketing
  - NDA provides information that informs the FDA decision in considering:
    - Drug safety and effectiveness in the proposed indications
    - Benefits and risks
    - Contents of package insert
    - Manufacturing methods
  - Stages
    - First stage
      - Investigational new drug (IND)
      - Based on pre-clinical data, typically from animal studies
    - Traditional approval requires "substantial" evidence of efficacy in controlled clinical trials
    - Trials leading to licensure are typically conducted in 3 phases
      - Phase 1 – healthy volunteers (sometimes patients) to determine toxicity
      - Phase 2 – dose escalation or other techniques to determine "optimal doses"
      - Phase 3 – large adequately controlled studies to show improvements in clinically relevant outcomes, compared with current drugs or placebo in the setting of no effective "standard of care" drug
  - The NDA should fully inform the agency about the drug
    - Toxicity profile
    - Results of clinical evaluations
    - Drug pharmacokinetics
    - Manufacturing information
  - The agency has 60 days to review NDA
    - If the NDA is acceptable, the agency will provide a standard (~10 months) or expedited (~6 months) review
    - Biologics are generally approved through a Biologic License Application (BLA) which is a broadly similar process
  - Process is complex, slow and extremely costly
    - Average cost to bring a new molecular entity to market is now estimated to be approximately $1.8 billion and is rising rapidly (*Nat Rev Drug Discov* 2010;9(3):203-214)
    - For hematology:
      - "Barrier to entry" will lead to a lack of new drugs particularly for more rare indications
      - Costs will drive drug developers away OR will result in catastrophically expensive medications
  - Drug innovation is going to require innovations not only in drug development but in the pathways of drug evaluation and approval
- Phase 4 research
  - "Post marketing phase" of a drug's lifespan – has been underutilized
    - Rigorously collecting data "after the approval" allows:

                - Increased data on safety (increases clinicians' confidence)
                - Collects data in divergent populations
                - May lead to new indications
            - Ongoing regulatory approval may be contingent upon the collection and provision of data in the post-approval period
        - "Post-marketing" monitoring and research may allow licensure of a drug which has not satisfied the traditional requirements for approval
        - What is a phase IV project
            - Traditionally: "pharmacovigilance"
            - Collected data on reported behavior of a product in a broad population
            - Examples
                - Summation of individual reports
                - Formal, but not product specific
                    - FDA's Mini-Sentinel program
                - Formal and specific
                    - AS a condition of ongoing approval
        - Example of outcome research – see *JAMA* 2004;29(21):2647-50 for cerivastatin and the problems with "case report based pharmacovigilance"
            - Need more data acquisition and analysis!
        - When properly done, Phase IV projects offer the potential to reliable collect data that could not be collected in any other way
            - Population exposure
            - Rare diseases and rare patients
            - New avenues for drug approval
            - New avenues for adverse event reviews
            - All rely on enhanced outcome event capture, either generically or specifically
        - Novel approaches to drug approval
        - Mitigating risk
            - REMS programs – ensure the benefits of a drug outweigh the risks (collection and dissemination of safety data)
        - The example of dabigatran (see *N Engl J Med* 2013;368(14):1272-4

Aplastic Anemia

Current Concepts in the Pathophysiology and Treatment of Aplastic Anemia – Neal S. Young

- Summary of pathophysiology
    - Immune-mediated bone marrow destruction
    - Stem cell loss occurring in aplastic anemia
    - Genetics of bone marrow failure in "acquired" aplastic anemia
- Components of treatment
    - Immunosuppressive therapy
    - Stem cell stimulation therapy
    - Supportive care strategies

Allogeneic BM Transplantation for the Treatment of Aplastic Anemia: Current Results and Expanding Donor Possibilities – Gerard Socie

- Transplantation from HLA-identical sibling donors
    - Conditioning regimen with Cy + ATG
    - Use of bone marrow as the source of stem cells
    - GVHD prophylaxis with CSA + MTX
    - Transplantation issues in patients < 40 years old vs. > 40 years old

    - cGVHD
    - Long-term complications
- Transplantation from unrelated donors

Management of the Refractory Aplastic Anemia Patient: What Are the Options? – Judith C. W. Marsh and Austin G. Kulasekararaj

- What does "refractory" aplastic anemia really mean?
- Treatment options
    - Unrelated donor HCT
    - If no donor is available
        - Repeat courses of ATG
        - Other immunosuppressive medications (alemtuzumab and cyclophosphamide)
        - Alternative donor transplantation (cord blood vs. haplo-identical HCT)
        - Other agents (eltrombopag and androgens)
- Supportive care in refractory SAA
    - Transfusion issues
        - Alloimmunization after transfusion
        - Use of irradiation products
        - Iron chelation – when to start and what to use
    - Infectious disease issues
        - Role of granulocyte transfusions
        - Best prophylaxis approach

Genomics in Hematology 101 for the Practicing Clinician

ABC's of Genomics – Stefan K. Bohlander

- Introduction to the human genome
- Variability of the human genome
    - Single nucleotide polymorphisms (SNPs)
    - Copy number variants
- Genome analysis methods
    - Cytogenetics and molecular cytogenetics and high-throughput array platforms
    - Sequencing
- Analysis of cancer genomes with next-generation sequencing (NGS)
- Whole exome sequencing (WES) vs. whole genome sequencing (WGS)
- Transciptome sequencing
- Gene panel sequencing
- Limitations of NGS
- Ethical considerations

Genomic Applications in the Clinic: Use in the Treatment Paradigm of Acute Myeloid Leukemia – Richard F. Schlenk and Hartmut Dohner

- Disease classification
- Prognostication of response to induction therapy
- Prognostication of relapse and OS
- Risk
    - Good risk
    - Intermediate risk
    - Poor and very poor risk
- Prognostication in first relapse

Genomic Stratification for the Treatment of Lymphomas – Sandeep S. Dave

- Diffuse large B-cell lymphoma
- Burkitt's lymphoma
- Chronic lymphocytic leukemia

Changing Paradigms in Acute Lymphoblastic Leukemia: From the Genome to the Patient

Targeting Signaling Pathways in Acute Lymphoblastic Leukemia: New Insights – Christine J. Harrison

- Cytogenetic subgroups and outcome
    - Good-risk cytogenetic abnormalities
    - Established poor-risk cytogenetic abnormalities
    - Recent identification of poor-risk abnormalities
        - iAMP21
        - IGH@ translocations
- Association of chromosomal abnormalities with age
- Genetic aberrations
    - CRLF2
    - IKZF1
- Treatment of certain aberrations

Pharmacogenomics of Acute Lymphoid Leukemia: New Insights into Treatment Toxicity and Efficacy – Mary V. Relling and Laura B. Ramsey

- Genomic variations and their association with risk of ALL and relapse of disease
- Variants associated with drug effects
    - Methotrexate efficacy and pharmacokinetics
    - Asparaginase efficacy and allergy
    - Osteonecrosis

New Immune Strategies for the Treatment of Acute Lymphoblastic Leukemia: Antibodies and Chimeric Antigen Receptors – Anjali S. Advani

- Recent data on therapies
    - Naked antibodies
        - Rituximab
        - Epratuzumab
        - Alemtuzumab
    - BiTE antibodies
        - Blinatumomab
    - Immunotoxins/Immunoconjugates
        - BL22 and CAT-8015
        - Combotox
        - SAR3419
        - Inotuzumab ozogamicin
    - Chimeric antigen receptors

Clinical Dilemmas in Acute Myeloid Leukemia

High-risk Acute Myelogenous Leukemia: Treatment Today … and Tomorrow – Gary J. Schiller

- Why is HR-AML a high risk disease?
- Risk stratification – refinements
- Current treatment strategies of HR-AML

    - Standard of care
    - Novel and investigational agents
        - Cytostatic agents – clofarabine, elacytarabine, CPX-351
        - Immunoconjugate – gemtuzumab ozogamicin
        - Other targeted agents – farnesyltransferase inhibitors, histone deactylase inhibitors, FLT3 antagonists
        - Chemosensitizing agent – CXCR4 antagonist

Core-binding Factor Acute Myeloid Leukemia: Can We Improve on HiDAC Consolidation? – Peter Paschka and Konstanze Dohner

- Treatment outcomes
    - Chemotherapy
    - Gemtuzumab ozogamicin
    - Allo-HCT
    - Salvage treatment for relapsed disease
- Genetic basis of CBF-AML
- Cooperating alterations
    - KIT
    - FLT3
    - RAS
- Monitoring of MRD

FLT3 Mutations in Acute Myeloid Leukemia: What is the Best Approach in 2013? – Mark Levis

- Testing for the FLT3 mutation
    - PCR assays
    - Limitations of assays
    - FLT3-ITD mutation length
    - Allelic ratio
    - Interactions with other genetic lesions
- How to treat FLT3-ITD AML
    - Role of transplant
    - Elderly patients
- FLT3 inhibitors
    - Midostaurin
    - Lestaurtinib
    - Sorafenib
    - Quizartinib
    - Ponatinib
    - PLX3397

Pediatric Hematology: Insights Applicable to All!

Treatment of Infant Leukemia: Challenge and Promise – Patrick Brown

- Characterization of infant leukemia
- Current treatment for infant leukemia
- Recent biological discoveries with novel therapeutic implications

Evidence-Based Mini-Review: Does Hematopoietic Stem Cell Transplantation Benefit Infants with Acute Leukemia? – Edward Allan R. Sison and Patrick Brown

- Highlights of studies using HCT in infants in CR1 with ALL or AML

Hemophagocytic lymphohistiocytosis: Pathogenesis and Treatment – Gritta E. Janka and Kai Lehmberg

- Clinical syndrome of HLH
- Genetic and acquired HLH
    - Pathogenesis
    - How to differentiate genetic from acquired
- Treatment of HLH

Novel Clinical Trials for Pediatric Leukemia: Lessons Learned from Genomic Analysis – Andrea Biondi and Giovanni Cazzaniga

- Lessons from current clinical ALL trials
- Genomic analysis to drive tailored therapy
- Identification of new genomic alterations with potential prognostic relevance
    - IKZF1and B-cell development gene deletions
    - CRLF2-JAK-STAT signaling
    - Alterations of genes
        - TP53
        - CREBBP
    - Identification of new BCR-ABL-1-like entities with potential therapeutic relevance
    - ETP-ALL
    - Host pharmacogenomics
- Implications for future clinical trial design

HIV in Hematology: What's New?

Pathogenesis and Clinical Implication of HIV-Related Anemia in 2013 – Amanda J. Redig and Nancy Berliner

- Clinical features and outcomes of anemia in HIV
- Multifactorial pathogenesis of anemia in HIV
- The inflammatory connection in HIV infection in the aging
- Unanswered questions in anemia and HIV

Update on the Treatment of HIV-Associated Hematologic Malignancies – Richard F. Little and Kieron Dunleavy

- The burden of hematologic cancers in patients with HIV infection
- Management of lymphoid and myeloid tumors in patient with HIV infection
    - BLBCL and BL
    - Primary DLBCL of the CNS
    - HL
    - Leukemias

Transplantation in HIV-Infected Subjects: Is Cure Possible? – John A. Zaia and Stephen J. Forman

- Auto-HCT for AIDS-related lymphoma
- Genetic modification of hematopoietic stem/progenitor cells for HIV/AIDS
- Allo-HCT in HIV/AIDS

Infectious Disease Complications Encountered by the Practicing Hematologist

Evidence-Based Approach to Treatment of Febrile Neutropenia in Hematologic Malignancies – Juan Gea-Banacloche

- Prevention of fever during neutropenia using antimicrobial agents
- Stratification according to risk

- Fever and neutropenia syndromes
    - First episode of fever
    - Persistent fever
    - Recurrent or recrudescent fever
    - Engraftment fever

Treatment of Fungal Disease in the Setting of Neutropenia – Thomas J. Walsh and Maria N. Gamaletsou

- Neutropenia as a key risk factor in the development of IFIs in patients with hematologic malignancies
- Specific IFIs associated with neutropenia and their treatment
    - Candidiasis
        - Oropharyngeal and esophageal candidiasis
        - Candidemia
        - Chronic disseminated candidiasis
    - Aspergillosis
    - Mucormycosis
    - Fusarium infections
    - Scedosporium infections
    - Infections caused by dematiaceous molds
    - Trichosporonosis
    - Malassezia infections

Multi-Drug Resistant Bacteria: What is the Threat? – Matteo Bassetti and Elda Righi

- How to treat resistant infections in hematological patients
    - Initial clinical assessment and risk factors for resistant infections
        - Main organisms
        - Mechanisms of resistance
        - Drugs not to use
    - Choice of empiric therapy regimens
    - Targeted therapy for severe infections in hematological patients
        - Modifications of initial therapy
        - Indications for de-escalation therapy
        - Dosage recommendations for the most common antimicrobials used for infections due to resistant organisms