Updates in Hematopoietic Stem Cell Transplantation or

“Ten Things I learned at ASH to share with you”

Richard T. Maziarz, MD
Professor of Medicine
January 14, 2011
Blood and Marrow Transplant Clinical Trials Network – BMT CTN

- *0101 Fungal Prophylaxis: vori vs flu completed
- *0102 MM: tandem auto vs auto/RIT allo completed
- 0201 PB vs BM completed
- #0202 Follicular lymphoma: auto vs allo closed
- *0301 Reduced Intensity Tx for Aplastic Anemia completed
- *0302 Primary GVHD Treatment - 4 arm phase II completed
- 0303 T-depleted Transplants for AML completed
- 0401 NHL: auto tx with BEAM + Rituxan vs Bexxar completed
- 0402 Sirolimus vs MTX + Tacrolimus for GVHD prophy completed
- 0501 Single vs Double cord in Ped completed
- 0502 Elderly AML in CR with RIT completed
- 0601 Unrelated tx for Sickle cell completed
- 0602 Scleroderma closed
Blood and Marrow Transplant Clinical Trials Network – BMT CTN

- 0603 RIT with haploidentical BM tx with post tx CTX
- 0604 UCB tx with RIT
- 0701 NST for Follicular Lymphoma
- 0702 MM randomized maintenance therapy trial
- 0703 SWOG Tandem auto tx for Rel/ ref HD
- 0801 Treatment of CGVHD
- 0802 Treatment of AGVHD- ph III- pred vs pred/MMF
- 0803 HSCT for HIV+ Lymphoma
- 0901 Randomized Conventional versus RIT for AML/MDS
- 0902 Stress reduction in transplantation patients
- 0903 ALLO HSCT for HIV+ malignancies
- 0904 CALGB/ CTN phase II multicenter RIT for CLL

*completed*
Selling points: TOM DELOUGHERY WROTE 2 CHAPTERS!!!
Multiple Myeloma
Multiple Myeloma Treatment Lines in Transplant-Eligible Patients

Frontline treatment

- Induction: Bz/Dex, Bz/Dex/Dox, Bz/Thal/Dex, Len/Dex
- Consolidation: SCT

Maintenance

- Observation: Thal, Thal/Pred

Relapsed

- Rescue: Bz, Bz/Liposomal Dox, Len/Dex

#1 Unresolved question: when should HSCT be utilized in the course of a myeloma patient

- SWOG 9321: Overall survival equivalent if used in patients with MM if auto HSCT used as consolidation of first chemotherapy induction (VAD → CTX mobilization) or at time of first progression (after months of VBMCP)
- In the biologic era???????
- Recently initiated French-American trial may shed insights on this issue
Melphalan/Prednisone/Lenalidomide (MPR) vs MEL200/ASCT Following Lenalidomide/Dexamethasone (Ld) Induction

Primary end point: PFS

Consolidation

MPR (n=202)
Melphalan: 0.18 mg/kg/d, days 1–4
Prednisone: 2 mg/kg/d, days 1–4
Lenalidomide: 10 mg/d, days 1–21 q 28 days ×6

Tandem MEL200
ASCT
stem cells mobilized with cyclophosphamide + G-CSF

No maintenance

Maintenance lenalidomide: 10 mg/d,
Days 1–21 q 28 days until relapse

n=402
<65 years

Lenalidomide: 25 mg, days 1–21
Low-dose Dex: 40 mg, days 1, 8, 15, 22 q 28 days ×4

MPR vs MEL200/ASCT Following Ld Induction: Differential Efficacy? - too early to tell

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<tr>
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<th>MPR</th>
<th>MEL200</th>
<th>( P ) Value</th>
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<td><strong>Induction, Best Response</strong></td>
<td>n=358</td>
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<tr>
<td>ORR</td>
<td>84%</td>
<td>92%</td>
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<tr>
<td>CR</td>
<td>5%</td>
<td>14%</td>
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<td>VGPR</td>
<td>32%</td>
<td>42%</td>
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<td><strong>Consolidation</strong></td>
<td>n=79</td>
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<tr>
<td>ORR</td>
<td>92%</td>
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<tr>
<td>CR</td>
<td>14%</td>
<td>25%</td>
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<tr>
<td>VGPR</td>
<td>42%</td>
<td>37%</td>
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<td>*<em>12-Month Survival</em></td>
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<tr>
<td>PFS</td>
<td>91%</td>
<td>91%</td>
<td>0.77</td>
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<tr>
<td>OS</td>
<td>97%</td>
<td>98%</td>
<td>0.27</td>
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</table>

*Median F/U = 9 months.

Outcome with lenalidomide plus dexamethasone followed by early autologous stem cell transplantation in the ECOG E4A03 randomized clinical trial.

David S Siegel¹, Susanna Jacobus², S. Vincent Rajkumar³, Rafat Abonour⁴, Natalie Callander⁵, Michael Katz⁶, Rafael Fonseca⁷, David H. Vesole¹ On behalf of the Eastern Cooperative Oncology Group

¹John Theurer Cancer Center, Hackensack, NJ; ²Dana-Farber Cancer Institute, Boston, MA; ³Mayo Clinic, Rochester, MN; ⁴Indiana University School of Medicine, Indianapolis, IN; ⁵University of Wisconsin, Madison, WI; ⁶International Myeloma Foundation, Los Angeles, CA; ⁷Mayo Clinic, Scottsdale, AZ;
E4A03: Landmark Analysis at Median Follow-up of 36 mo

431 patients alive at 4 cycles

Off therapy at 4 cycles
n=183

- no transplant
  N=93 (median age 68)
- Transplant
  n=90 (median age 57)

Primary therapy beyond 4 cycles
n=248

- Ld
  n=140 (median age 66)
- LD
  n=108 (median age 65)

Rajkumar SV et al. The Lancet Oncology, Volume 11, Issue 1, Pages 29 - 37, January 2010
Outcomes in pts Age <70

Progression Free Survival

Overall Survival
Outcome in pts Age ≥70

Progression Free Survival

Overall Survival
Toxicities

• Patients who discontinued the assigned therapy at 4 cycles were censored. Unable to assess treatment related morbidity.
• Given that the overwhelming majority of deaths occurring within 1 year were treatment related, this should be a good surrogate for TRM.

1-yr mortality

<table>
<thead>
<tr>
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<th>No Early SCT:</th>
<th>Early SCT</th>
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<tr>
<td>Overall</td>
<td>0.94 (0.91, 0.96)</td>
<td>0.99 (0.97, 1.00)</td>
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<td>Age &lt;65</td>
<td>0.94 (0.90, 0.98)</td>
<td>0.99 (0.96, 1.00)</td>
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<tr>
<td>65≤ Age &lt;70</td>
<td>0.96 (0.91, 1.00)</td>
<td>0.94 (0.83, 1.00)</td>
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<td>Age ≥70</td>
<td>0.92 (0.88, 0.97)</td>
<td>1.00 (1.00, 1.00)</td>
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#2: Should patients with MM consider early allogeneic HSCT?

- SWOG 9321: high early TRM but 30% PFS at 7 yrs
- Gratwohl, EBMT: TRM in allo MM decreased from ~ 50→25% from 1995→ 2001; likely consequence of improved supportive care
- Advent of reduced intensity transplantation could further reduce TRM
Tandem AutoHCT with or without Maintenance Therapy (auto-auto) versus Single AutoHCT Followed by HLA Matched Sibling Non-Myeloablative Allogeneic HCT (auto-allo) for Patients with Standard Risk Multiple Myeloma: Results from the BMT-CTN 0102 Trial


On behalf of the Blood and Marrow Transplant Clinical Trials Network

National Heart Lung and Blood Institute
National Cancer Institute
Introduction

• The prognosis of patients with high-risk myeloma (HR MM) continues to be poor, despite the early incorporation of novel agents.

• Early phase trials of allo HCT suggest the possibility of an immunologic graft-versus-myeloma effect that might favorably affect survival.

• Less toxic nonmyeloablative preparative regimens allow more widespread use of alloHCT in the MM population.
BMT CTN 0102

• Phase III multicenter trial comparing tandem autologous HCT (auto-auto) to an autologous HCT followed by a non-myeloablative allogeneic HCT (auto-allo).

• 710 patients from 43 US centers were enrolled from December 2003 to March 2007.

• Assignment to auto-allo was determined by availability of an HLA-matched sibling donor.

• High Risk was defined as chromosome 13 deletion by metaphase karyotype and beta-2 microglobulin > 4mg/L.

• Primary endpoint-3-year progression-free survival in the standard risk group.
1st Autologous Transplant
N=710

- No Sibling Donor
  - Auto-Auto
    - High Risk
      N=48
    - Standard Risk
      N=436
  - Standard Risk
    N=189

- Sibling Donor
  - Auto-Allo
    - High Risk
      N=37
Survival Outcomes after the First Transplant: Auto-Auto vs. Auto-Allo: Intent-to-treat analysis

Progression-free Survival

Auto/Auto, 46% @ 3yr
Auto/Allo, 43% @ 3yr

p-value = 0.67

Overall Survival

Auto/Auto, 80% @ 3yr
Auto/Allo, 77% @ 3yr

p-value = 0.19

Survival Outcomes after the First Transplant: Auto-Auto vs. Auto-Allo: Intent-to-treat analysis

# at risk:

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<td>348</td>
<td>292</td>
<td>242</td>
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<td>178</td>
<td>154</td>
<td>123</td>
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<tr>
<td>Auto/Allo</td>
<td>189</td>
<td>165</td>
<td>138</td>
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<td>105</td>
<td>89</td>
<td>71</td>
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</table>
Cumulative Incidence of Disease Progression/Relapse and Treatment-Related Mortality after First Transplant

- **Progression/Relapse**
  - Auto/Auto, 46% @ 3yr
  - Auto/Allo, 40% @ 3yr

- **Treatment-related Mortality**
  - Auto/Auto, 4% @ 3yr
  - Auto/Allo, 12% @ 3yr

P-value = 0.41

P-value < 0.001

Cumulative Incidence, %

[Graph showing cumulative incidence over months for progression/relapse and treatment-related mortality]
Causes of death according to treatment arms

Auto-Auto
- Myeloma, 70%
- Organ Failure, 15%
- Infection, 2%
- Other, 12%
N=100, 23%

Auto-Allo
- Myeloma, 38%
- Organ Failure, 19%
- Infection, 17%
- IPS, 6%
- ARDS, 4%
- GVHD, 11%
- Graft Failure, 2%
- Other, 3%
N=52, 27%
Tandem AutoHCT with or without Maintenance Therapy (auto-auto) versus Single AutoHCT Followed by HLA Matched Sibling Non-Myeloablative Allogeneic HCT (auto-allo) for Patients with **High Risk** Multiple Myeloma: Results from the BMT-CTN 0102 Trial


On behalf of the Blood and Marrow Transplant Clinical Trials Network
Autologous Transplant
N=710

No Sibling Donor
Auto-Auto
N=484

Sibling Donor
Auto-Allo
N=226

Standard Risk
N=436

High Risk
N=48

High Risk
N=37

Standard Risk
N=189

Groups being compared
Survival Outcomes after the First Transplant: Auto-Auto vs. Auto-Allo: Intention-to-treat analysis

Progression-Free Survival
- Auto/Allo, 40% @ 3yr
- Auto/Auto, 33% @ 3yr

Overall Survival
- Auto/Allo, 59% @ 3yr
- Auto/Auto, 67% @ 3yr

P-value = NS
Cumulative Incidence of Disease Progression/Relapse and Treatment-related Mortality after the First Autologous Transplant

**Progression/Relapse**

- Auto/Auto, 50% @ 3yr
- Auto/Allo, 30% @ 3yr

**Treatment-related Mortality**

- Auto/Auto, 11% @ 3yr
- Auto/Allo, 24% @ 3yr

P-value = 0.09

P-value = NS
Impact of Chronic GVHD on Disease Progression/Relapse: Patients with Standard Risk Disease

*Landmark analysis at 12 months after the allogeneic transplant.
Survival Outcomes of Auto-Auto vs. Auto-Allo after the First Autologous Transplant: Combined Standard and High Risk Cohorts

- Progression-Free Survival
- Overall Survival

Auto/Auto (n=484), 79% @ 3yr
Auto/Allo (n=226), 75% @ 3yr

Auto/Auto (n=484), 45% @ 3yr
Auto/Allo (n=226), 42% @ 3yr

P-value = NS
Conclusion:

- Allogeneic HSCT is not currently considered as front line therapy for patients with multiple myeloma
- Allogeneic HSCT may remain beneficial as late salvage option
#3: Is there a role for maintenance therapy for patients with MM after autologous HSCT?

• In non-transplant and chemotherapy induction setting, prednisone 50 mg qod had benefit in improved PFS and OS over 10 mg qod

• Various studies had variable results re: efficacy of maintenance after autologous HSCT; dexamethasone and/or thalidomide generally used
CALGB 100104

A Phase III Randomized, Double-Blind Study of Maintenance Therapy With Lenalidomide (CC 5013) or Placebo Following Autologous Stem Cell Transplantation for Multiple Myeloma

Philip McCarthy, Roswell Park Cancer Institute, representing CALGB, ECOG and BMT CTN
Stage 1–3, <70 years
Therapy at least 2 cycles
Stable disease or better
≤1 year from Rx initiation
$2 \times 10^6$ CD34 cells/kg

Registration

Restaging
Days 90–100

Mel 200
ASCT

CR
PR
SD

Placebo

Lenalidomide
10 mg/d with ↑↓
(5–15 mg)

Stratification based on Diagnostic B2M and IMiD Use during Induction

Objectives

• Primary Objective:
  – Determine the efficacy of lenalidomide in prolonging time to progression (TTP) in myeloma patients following ASCT
  – Powered to determine a prolongation of TTP from 24 months to 33.6 months (9.6 months)

• Secondary Objectives:
  – CR rate post-ASCT
  – PFS and OS
  – Feasibility of long-term lenalidomide administration
Accrual

- Target Accrual: Register 538 with a goal of 462 randomized based on 10% drop out rate
- First enrollment in April of 2005
  - CALGB: n=376; ECOG : n=133; BMT CTN: n=59
- Closed in July of 2009: 568 registered pts from 47 Centers
- Drop out rate before randomization is 19%
  - PD/NR (16%), AEs (5%), Died during Rx (2%), Refusal (26%), Other disease (1%), Other Rx (4%), Other reasons (33%), Unknown (14%)
- Patients continued on therapy until progression
- Majority of patients received thal/ len + dexamethasone induction
Results

• There was a benefit between lenalidomide over placebo in each stratification
• 86 of ~ 110 eligible placebo patients started lenalidomide therapy
• As of November 2010, 122 lenalidomide patients and 86 placebo patients remain on lenalidomide
• 25 new malignancies reported so far
  – 4 before randomization
  – 15 of 231 on lenalidomide arm
  – 6 of 229 on the placebo arm
• Of the 25 new malignancies, there are 5 cases of AML/MDS
  – 2 MDS cases did not receive lenalidomide
  – Of 3 MDS/AML lenalidomide pts, 1 received breast cancer therapy in the past
CALGB 100104, follow up to 12/17/2009

ITT Analysis with a Median Follow-up from transplant of 17.5 months (p < 0.0001)
13 deaths in lenalidomide arm and 24 deaths in the placebo arm (p<0.052) There may have been a difference between the 2 arms which may no longer be present due to cross-over

ITT Analysis: OS based on follow-up forms submitted on or before 12/17/2009
Conclusions

- Maintenance therapy with lenalidomide when compared to placebo will significantly prolong time to disease progression.

- Currently, there is no difference in OS at a median follow-up of 1.5 years post-ASCT.

- Lenalidomide prolonged TTP within patient stratification by high and low β2M, and prior thalidomide or lenalidomide induction therapy.

- Lenalidomide maintenance produced some hematologic toxicity, but this was not severe with dropouts due to all AEs at 12%.
#4 Did Wall Street get it right?
#4 Did Wall Street get it right?

• “Celgene (CELG) shares lost over 8% in regular trading to close at $55.64 on Monday after the company released clinical data for its multiple myeloma drug, Revlimid, at the American Society of Hematology (ASH) over the weekend. The stock lost another 3% after hours.”

• “The main concern brought up at ASH was data suggesting prolonged use of Revlimid increased the risk of developing secondary malignancies. Data presented from a study of Revlimid in long-term maintenance therapy showed 15 cases of secondary malignancies in Revlimid patients compared to six cases of secondary cancer in placebo patients.

• Perhaps more damaging was a pooled analysis of three studies involving 1060 patients compiled by ISI Group biotech analyst Mark Schoenebaum. Patients on long-term Revlimid treatment were associated with 32 secondary cancers, or 5.9%, compared to 9 secondary cancers, or 1.7%, in patients on placebo.”

• Source: SEEKING ALPHA- web bulletin (one of many)
#5: Amyloidosis: are outcomes improving or is selection getting better?
Autologous HSCT for AL amyloidosis, Gertz et al, 2010

• 434 pts auto tx between 1996-2010
• Most critical determinants of outcome: stage of amyloidosis
• Factors that can influence stage: BNP and troponin levels
• Targets: nt-proBNP <332 and troponin < .035
• Staging I- both low; II- single elevation; III- both elevated
• Also clonal free light chain level predicted
Autologous HSCT for AL amyloidosis, Gertz et al, 2010

Cardiac: Stage 1-3 stratified by BNP/Troponin

Differential of involved Free light chains < or > 13.5 mg/dl
Autologous HSCT for AL amyloidosis, Gertz et al, 2010

Other presentations:
1. Outcomes since 2006 are improved, primarily associated with lower TRM in first 100 days
2. Higher plasma cell burden on presentation (>10%) had worse outcomes, mostly due to higher cardiac burdens
3. Response to autologous HSCT correlates with survival
Mayo Clinic: Retrospective analysis: Post auto HSCT response correlates with survival in pts with amyloidosis
Does auto HSCT remain an option for patients with T cell lymphoma?

- CIBMTR analysis, Smith et al, #689
- Retrospective analysis: 241 pts with T-NHL
- Autologous: n = 115
- Allogeneic: n = 126

- Current belief: no benefit of auto tx in T-NHL
Does auto HSCT remain an option for patients with T cell lymphoma?

• Heterogenous population: CR1, CR2, resistant; ALCL vs PTCl vs AILD vs Other; # lines of treatment 1->5; conditioning; etc

• Univariate analysis @ 3yrs
  – TRM : Auto 15% / Allo 29%
  – Relapse/progress: Auto 56% / Allo 38% *
  – PFS: Auto 29% / Allo 33%
  – OS: Auto 45% / Allo 42%

• Multivariate analysis
  – TRM RR 3.031 for allo*
  – Relapse RR .504 for allo*; 4.696 for chemo resis*
  – Treatment failure RR .815 for allo
  – Overall mortality RR .920 for allo; 3.144 for chemo resis*

• * p < .05

• Conclusions: Allogeneic tx has higher TRM but may reduce relapse risk; for some selected pts, autologous HSCT may provide equivalent OS

• Caveats: Retrospective registry studies can be flawed by heterogeneity of patient populations and restricted for review by submitted data
#7: Can patients with systemic lymphoma involving CNS anticipate any benefit with autologous stem cell transplantation
CNS Remission at the Time of Autologous Stem Cell Transplantation Improves Outcomes for Patients with Non-Hodgkin Lymphoma with Pre-existing CNS Involvement

A CIBMTR Analysis

(Abstract #371)
Outcomes after Autologous Transplant (AHCT) for those with Pre-existing CNS Lymphomatous Involvement

• **AHCT: Single institution: small series**
  – MDACC- patients with CNS involvement at relapse had poor outcomes, Van Besien, JCO, 1996
  – Stanford – CNS disease control → OS 41% @ 5yrs, Alvernas, BBMT 2000
  – Johns Hopkins – pre-existing CNS disease is no contraindication to Tx but negative prognostic factors can be identified, Kasamon, BBMT, 2005
  – EBMT – CNS disease at relapse & active CNS disease at time of transplant are associated with poor outcomes, Williams, JCO, 1994

• **Outcomes with non-transplant therapy- NHL with CNS parenchymal relapse**
  – PCNSLSG study- best outcomes achieved with age< 60 and high dose methotrexate (MTX); med OS = 1.6 yrs, Doolittle, Blood, 2008
Methods

• **Patients:**
  
  • AHCT for NHL reported to CIBMTR
    - 151 adults with CNS involvement prior to transplant
      - Parenchymal/ epidural/ leptomeningeal involvement
    - 4688 adult pts without CNS disease
    - AHCT between 1990-2005
    - Primary CNS Lymphoma excluded

• **Outcome measures:**
  - Non Relapse Mortality (NRM)
  - Relapse/ progression
  - Progression free survival (PFS)
  - Overall survival (OS)
CNS+ Patient Population

- # pts (1990-2005) 151
- Median age 46
- Male sex 64%
- Histology
  - Follicular 15%
  - DLCL 37%
  - High Grade 22%
- Immunophenotype- B 93%
- CranialSpinal XRT as part of Rx 31%
- CNS involvement
  - Parenchymal 36
  - CSF 59
  - Epidural space 55
Variables Analyzed

• **Patient-related**
  – Age
  – Gender
  – KPS

• **Transplant-related**
  – Year of transplant
  – Interval from diagnosis to AHCT
  – Interval from relapse to AHCT
  – Length of first remission
  – Conditioning regimen
  – Stem cell source
  – Irradiation in conditioning
  – Rituximab usage
  – Planned post-transplant XRT

• **Disease-related**
  – Histology
  – Second line IPI at AHCT
  – Stage
  – LDH
  – Immunophenotype
  – B symptoms
  – Extranodal sites
  – Pre-transplant therapy
  – CNS irradiation
  – Disease status at transplant
  – CNS disease status at time of transplant
Univariate Analysis

• **CNS⁺** cohort:
  – Younger age group
  – Lower performance status
  – Higher IPI
  – Advanced stage
  – More aggressive histology
  – Higher number extranodal sites
  – Shorter interval between dx and auto tx
  – Higher likelihood of relapse within CNS

• No significant differences:
  – Sex, immune phenotype, B symptoms, BM involvement, # therapy courses, Rituximab exposure, conditioning regimens, disease status at transplantation, KPS at date of last contact
## Univariate Analysis: Outcomes at 5 Years Post AHCT

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<th>Outcome</th>
<th>Non-CNS</th>
<th>CNS</th>
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<tr>
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<td>57%</td>
<td>61%</td>
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<tr>
<td>NRM</td>
<td>8%</td>
<td>9%</td>
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<tr>
<td>DFS</td>
<td>35%</td>
<td>30%</td>
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<tr>
<td>OS</td>
<td>49%</td>
<td>42%</td>
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Univariate analysis: Pre-transplant CNS Status and Outcomes
CNS remission vs. No CNS remission

RELAPSE
P<0.001

Prob of PFS
P<0.001

Prob of OS
P<0.001
Multivariate Analysis- Case-Control Study: Outcomes in Preexisting CNS\(^+\) vs CNS\(^-\) AHCT

- Imbalance of risk factors in CNS\(^+\) cohort
- Propensity score matching based on risk factors:
  - Age, histology, IPI score, disease status at tx, year of tx, interval from dx\(\rightarrow\) tx
- Numerical Propensity score generated for each patient
- Matched controls (\(\sim\) 97% with 4 controls per patient) selected with closest matched propensity score
- 135 CNS\(^+\) pts matched with 535 CNS\(^-\) pts
Outcomes of AHCT for NHL with Pre-existing CNS Cases vs Matched Non-CNS Involvement Controls

- **NRM**
  - CNS (n=135)
  - Non-CNS (n=535)
  - p = .8968

- **RELAPSE**
  - CNS (n=135)
  - Non-CNS (n=535)
  - p = .5572

- **Prob of PFS**
  - CNS (n=135)
  - Non-CNS (n=535)
  - p = .6152

- **Prob of OS**
  - CNS (n=135)
  - Non-CNS (n=535)
  - p = .2469
Summary

• No statistically significant differences in NRM, Relapse, DFS and OS in pts with pre-existing CNS NHL undergoing auto HSCT compared to those with no prior CNS disease.

• Patients with active CNS disease at time of transplant have diminished PFS & OS

• CNS remission is a priority for pts who pursue AHCT for NHL. If achieved, excellent long-term survival can be achieved even in the setting of adverse baseline prognostic factors.
#8 Are there innovations in transplantation for AML?

• Practice algorithms:
  – Low risk: chemotherapy only
  – High risk: transplantation
  – Intermediate risk: ?????

• Auto vs allo vs chemo ➔ all are viable options
# 367: HOVON/SAKK phase III trial of ANLL pts in CR1

- **Pt population:**
  - 519 pts with ANLL in CR1 after 2 cycles of consolidation therapy
  - Age ≤ 60
  - Not eligible for allo HSCT

- **Randomized to M+ E consolidation vs BU/cy conditioned auto tx**
  - Matched population; ~80% intermediate risk pts in either arm
  - Med f/u over 8 yrs
Results: HOVON/SAKK phase III trial of ANLL pts in CR1

- 1. Recovery of ANC and plts * autotx
- 2. NRM 4% Auto tx; 1% chemo
- 3. RFS @ 5 yrs 39% vs 29% *auto tx
- 4. OS @ 5 yrs 44% vs 40%

→ Salvage by late allo/auto HCST 40% of chemo/18% of primary cohort of auto tx

- Relapsed pts 5 yr survival
  - 30% if salvage with HCST
  - 3% if salvage with chemo only

* = statistically significant advantage
Summary: Hovon/ SAKK trial

- Autologous HCST remains viable option for ANLL pts
- RFS but not OS impacted
- Cost:benefit decision analysis studies may be performed in the future to better assist in decision making re: determination of optimal management algorithms
#9: Innovations in HSCT

**Ex vivo expansion of cord blood**

- Limitations of HCST options for some patients remain
- Unrelated donor pool still limited, particularly for minorities and mixed populations
- UCB HCST is associated with lower GVHD rates but limitedlogistically due to ability to collect fetal blood from discarded placental product, despite higher CD34+ populations
- Double cord HCST has emerged as viable option for adults with lack of available donors
Umbilical cord blood (UCB) as a source of hematopoietic stem cells for hematopoietic reconstitution

**Advantages**
- Rapid procurement
- Less stringent HLA matching
- Expanded donor pool
- Less graft-versus-host disease

**Disadvantages**
- Low cell dose
- Delayed engraftment
- Poor immune reconstitution
- Increased graft failure rate

**Potential Solutions:**
- *Double Cord Transplantation*
- *Ex Vivo Expansion*

Mesenchymal Stem Cell (MSC) Based Cord Blood (CB) Expansion Leads to Rapid Engraftment of Platelets and Neutrophils.

1M de Lima, 1S N Robinson, 1J McMannis, 1A Alousi, 1R Saliba, 1M Munsell, 1P Kebriaei, 1C Hosing, 1S Parmar, 1L Cooper, 1N Shah, 1S Kelly, 1G Rondon, 1M Fernandez-Vina, 1I Maewall, 1D Bosque, 2C M Bollard, 1J Chen, 3I McNiece, 3K V Komanduri, 1Y Nieto, 1R Jones, 1B S Andersson, 1U Popat, 1R Champlin, 4P J Simmons and 1E J Shpall.

1University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA. 2Baylor College of Medicine Center for Cell and Gene Therapy, Houston, Texas, USA. 3University of Miami, Miami, FL 4The Centre for Stem Cell Research, Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases, University of Texas Health Science Center at Houston, Houston, Texas, USA.
Current ex-vivo expansion protocols: 

Limitations and areas for improvement

• Current protocols are based on establishing cultures with highly CD34+ or CD133+ enriched populations of hematopoietic stem/progenitor cells.

  Shpall et al. BBMT 2002  
  de Lima et al. BMT 2008 / ASH 2008  
  Delaney C et al. Nat Med. 2010 Feb;16(2):232-

• Prior ex vivo expansion techniques have resulted in significant losses of hematopoietic progenitors prior to expansion.

  McNiece, McMannis, Shpall. BBMT 2002

• Suspension culture in cytokines does not recapitulate the physiology of the bone marrow microenvironment (niche).
Mesenchymal Stem Cells (MSC)

- MSC are a stromal component of the hematopoietic microenvironment.

- They provide cellular and extracellular components of the stem cell “niche”.

- When isolated and used *in vitro* in combination with other factors added during *ex vivo* culture, MSC markedly increase the expansion of CB hematopoietic progenitor cells (HPC).

*Robinson et al. Bone Marrow Transplantation (2006) 37, 359*
Hypothesis

Double cord blood transplant in which one unit is ex-vivo expanded in MSC-based co-culture will lead to faster hematopoietic engraftment.
### Preparative regimen

<table>
<thead>
<tr>
<th>Day</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>-9</td>
<td>Hydration Therapy</td>
</tr>
<tr>
<td>-8</td>
<td>Melphalan 140 mg/m²</td>
</tr>
<tr>
<td>-7</td>
<td>Thiotepa 10 mg/Kg</td>
</tr>
<tr>
<td>-6</td>
<td>Fludarabine 40 mg/m²</td>
</tr>
<tr>
<td>-5</td>
<td>Fludarabine 40 mg/m²</td>
</tr>
<tr>
<td>-4</td>
<td>Fludarabine 40 mg/m² Rabbit-ATG</td>
</tr>
<tr>
<td>-3</td>
<td>Fludarabine 40 mg/m² Rabbit-ATG</td>
</tr>
<tr>
<td>-2</td>
<td>Rest</td>
</tr>
<tr>
<td>-1</td>
<td>Rest</td>
</tr>
<tr>
<td>0</td>
<td>CB Infusions</td>
</tr>
</tbody>
</table>

### GVHD Prophylaxis:
**Tacrolimus and MMF**

Day 0
Infuse unmanipulated CB (CB#2) AND
*Ex vivo* expanded CB (CB#1)

Day -14
Thaw & wash CB#1

Day -8 to -2
**High-Dose Therapy**

**G-CSF**

**Ex vivo** CB#1-MSC co-culture expansion for 14 days
Engraftment and GVHD data

Median time to engraftment (range)

- Neutrophil (>500/µl) 15 days (range, 9-42)
- Platelet (>20,000/µl) 40 days (range, 13-62)

Cumulative Incidence of Engraftment

- Neutrophil (>500/µl) 97% (n=31)
- Platelet (>20,000/µl) 81% (n=26)

- One patient died before engraftment.
Chimerism – long-term engraftment from unmanipulated cord in most patients

- Of 28 evaluable patients, 15 (53%) showed evidence of hematopoiesis from the unmanipulated CB unit ONLY at day 21 - 30.

- 13 patients (47%) had hematopoiesis derived from both CB units (UNM predominant in 9 while in 4 EXP unit predominated).
Overall Survival

Median follow-up is 9.8 months (range 5.6 to 25.0 months).

Cumulative Incidence of acute GVHD

grade II-IV 50%
grade III-IV 16%
Chronic 6%
Conclusions

• To date, no infusional toxicity has been associated with transplantation of *ex vivo* expanded cord blood as part of a double CB transplantation protocol.

• The rapid neutrophil and platelet engraftment observed is likely a consequence of transplanting large numbers of lineage-committed hematopoietic progenitor cells derived from the *ex vivo* expanded CB unit.

• Our results provide the basis for a randomized comparison of double unmanipulated CBT *versus* double CBT in which one unit is *ex vivo* expanded as described here.

• Options for the future continue to emerge
#10: The uncertainty of GVHD-still driving us crazy after all these years

- Abst # 675: Paczesny et al., ASH 2010: BLOOD, 2009
- The holy grail of allotx is to identify biomarker profile, before aGVHD emergence with strong correlation to prognosis
- Predictive model of aGVHD suggested, based on expectations of unrelated allogeneic tx
- Proteonomics → 3 biomarkers (IL2Ra, TNFR1, elafin)
- Day 7, 14 assessments: elevations will predict aGVHD with 75% specificity; 57% sensitivity
- Preemptive therapeutics??????
2011 and beyond

The OHSU pursuit:
“Can adherent stromal stem cells provide efficacious adjunctive therapy in hematopoietic stem cell transplantation”?

Hematopoiesis support
GVHD prophylaxis
GI tract regeneration
Bronchiolitis obliterans therapy
Thanks for your attention and the trust you have in letting us share the care of your patients.