Allogeneic Hematopoietic Stem Cell Transplantation: State of the Art in 2019

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Overview of Talk:

• Update on allogeneic transplantation for malignant and nonmalignant diseases: state of the art in 2019
  – Updates on Disease Specific Survival after Transplantation
  – Myeloablative vs Reduced intensity transplantation for AML/MDS
  – Haplo transplants using posttransplant cyclophosphamide
    • Optimal graft source?
    • Who is the optimal haplo donor?
  – New approaches to managing disease relapse after transplantation
  – TPO mimetics to manage poor engraftment after transplantation
There Have Been Major Improvements in Transplant Outcomes Over the Past 2 Decades

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Major Improvements in Transplant Outcomes Over the Past 2 Decades

• First FDA approved drug (2016) to treat chronic GVHD
  – Ibrutinib demonstrated ORR 67% (CR=21%, PR=45%)
    • Miklos, D et al, Blood-Sept 2017

• New FDA approved drug (2017) to prevent CMV reactivation post-HCT
  – Letermovir- a non-nucleoside CMV inhibitor targeting viral terminase complex preventing viral replication (Marty F. et al. NEJM Dec 2017)
  – Reduced risk of CMV reactivation from 41% to 17% compared to placebo
Transplant Numbers Continue to Increase in the U.S.

Annual Number of HCT Recipients in the US by Transplant Type

CIBMTR Data 2018
Indications for an Hematopoietic Cell Transplant (HCT) and Donor Source in the U.S.

Selected Disease Trends for Allogeneic HCT in the US

Allogeneic HCT Recipients in the US, by Donor Type
In the era of precision medicine, why do we still perform these dangerous allogeneic transplants?

- Remains only curative modality for certain diseases associated with short survival with conventional therapy
  - Relapsed AML
  - Relapsed ALL
  - High Risk MDS

- Is the only curative modality for many non-malignant debilitating diseases
  - Sickle cell Anemia
  - Aplastic Anemia - Relapsed refractory to IST
Allogeneic Transplant For Hematological Malignancies

**Survival after HLA-Matched Sibling Donor HCT for AML, 2005-2015**

- Early (n=8,254)
- Intermediate (n=2,089)
- Advanced (n=2,766)

Probability, %

Years

**Survival after HLA-Matched Sibling Donor HCT for ALL, Age ≥18 Years, 2005-2015**

- Early (n=3,029)
- Intermediate (n=869)
- Advanced (n=437)

Probability, %

Years

**Survival after Allogeneic HCT for Follicular Lymphoma, 2005-2015**

- HLA-Matched Sibling, Sensitive (n=781)
- Unrelated Donor, Sensitive (n=710)
- HLA-Matched Sibling, Resistant (n=123)
- Unrelated Donor, Resistant (n=143)

Probability, %

Years

**Survival after Unrelated Donor HCT for Myelodysplastic Syndrome (MDS), 2005-2015**

- Early (n=1,697)
- Advanced (n=3,081)

Probability, %

Years
Reduced Intensity Conditioning (RIC): Decreases Risk Of TRM But May Increase Risk of Relapse For Some Malignancies

Possibility of increased risk of relapse (i.e. AML, MDS) with reduced intensity transplants

TRM= Transplant Related Mortality
Trial: Myeloablative vs. Reduced Intensity Allogeneic Transplantation for AML/ MDS

• **Hypothesis:**
  – **Alternative:** The lower treatment-related mortality (TRM) with reduced-intensity conditioning (RIC) would result in improved overall survival (OS) compared with myeloablative conditioning (MAC).
  – **Null:** Higher relapse with reduced-intensity conditioning (RIC) would result in inferior overall survival (OS) compared with myeloablative conditioning (MAC).

• **Study Design:**
  – Phase III randomized trial comparing MAC with RIC in patients with acute myeloid leukemia or myelodysplastic syndromes.

• **Patients:**
  – age 18 to 65 years
  – HCT comorbidity index ≤ 4
  – < 5% marrow myeloblasts pre-HCT

Scott et al JCO 2017
Myeloablative Versus Reduced-Intensity Hematopoietic Cell Transplantation for Acute Myeloid Leukemia and Myelodysplastic Syndromes

Scott et al JCO 2017
Graft Donor Sources - who to choose?

1) HLA Identical Sibling (SIB)
2) 8/8 Allele Matched Unrelated Donor (MUD)
3) alternative donors: see below

- HLA-Haploidentical related donor (Haplo)
- Cord Blood transplant
- 7/8 Allele Matched Unrelated Donor (MMUD)
Haploidentical Transplant For AML With Post-Transplant Cyclophosphamide; Results Comparable to MUD Donors

Survival

Figure 3. Overall survival. (A) The probability of OS by donor type after myeloablative conditioning regimen, adjusted for age and disease risk index. (B) The probability of OS by donor type after reduced intensity conditioning regimen, adjusted for disease risk index and secondary AML.
PBSC vs BM Following Haplo-Transplantation with Post-transplant Cytoxan

681 haplo-transplant pts

N=481 bone marrow
N=191 PBSC

Transplant Related

PB = Peripheral Blood
BM = Bone Marrow

Grade 2-4 aGVHD

Grade 3-4 aGVHD

Chronic GVHD

Bashey et al. JCO 2017
PBSC vs BM Following Haplo-Transplantation with Post-transplant Cytoxan

Survival

- BM and PBSC both viable stem cell options post Haplo transplant
- Longer follow-up needed to discern if PFS advantage with PBSC improves survival

Progression Free Survival

Bashey et al. JCO 2017
Choosing the Optimal Haplo Relative

**Fact:** In transplants from HLA matched donors (related and unrelated), best outcomes are associated with
- Donors that have the best HLA match
- Donors who are younger (<30 years MUD)
- Avoiding a female donor into a male recipient (results in less GVHD)

**Fact:** Recipients of Haplo Transplants may have many potential family donors to choose from

**Question:** Who would be an optimal related haplo donor - data currently not available to answer
- Does better HLA matching with Haplo donors matter?
- Whether a child haplo donor would be better than a sib or parent?
- Does haplo donor age matter?
  - Should we be choosing the youngest haplo donor available like a MUD?
- Does gender matching make a difference with haplo transplants?

**EBMT analysis:**
- 484 adult lymphoma patients
- 35% females
- Median age 41 years; range 18-72
- Disease:
  - Hodgkin lymphoma (HL-240; 51%)
  - Peripheral T cell lymphoma (PTCL-88; 19%)
  - Diffuse large B cell lymphoma (DLBCL-77; 16%)
  - Mantle cell lymphoma (MCL-40; 8%)
  - Follicular lymphoma (FL-29; 6%),
- Haploidentical SCT (haploSCT) with ptCy between 2010 and 2016 at EBMT participating centers.
- Median follow-up of alive patients was 32 months (range 3-93).
95% successful engraftment
  - Use of peripheral blood stem cells (PBSC) positively affected engraftment (HR=1.53; p<0.001).

Acute GVHD (AGVHD) grade II-IV 32%
AGVHD III-IV 8%
  - multivariate analysis PBSC use HR=2.1 p<0.001 for grade II-IV
  - multivariate analysis PBSC use HR=4.5 p=0.001 for grade III-IV.

The 2-year cumulative incidence of chronic GVHD (cGVHD) and extensive cGVHD were 25% and 9%, respectively.
  - MVA, use of a male donor was protective for cGVHD and extensive cGVHD (HR= 0.6 p=0.02; and HR 0.3 p=0.008, respectively).
(Ali Bazarbachi et al: Abstract 484)

Conclusions:

• The use of PBSC significantly improves engraftment but increases the risk of acute GVHD.

• PFS and OS are mostly influenced by disease characteristics (i.e. disease status and lymphoma subtype)

• The use of female donors increases the risk of chronic GVHD.

• PFS and survival was not impacted by donor age, gender, relationship of the donor to the recipient, degree of HLA mismatch or ABO incompatibility, prior donor pregnancy

• These data support the concept that any haplo-identical family member can be used as a donor (avoiding DSA).

(Ali Bazarbachi et al: Abstract 484)
1976-2013, period transplants conducted
4,315 pts transplanted for hematological diseases single intuition (City of hope)
Diagnoses- acute leukemia (54%), chronic leukemia (17%), lymphoma (11%), myelodysplastic syndrome (10%), severe aplastic anemia (5%), and other hematologic diseases (3%);
median age at HCT was 38.5y (0.3-75.4).
As of December 31, 2014
- 1841 patients were still alive in whom the median follow-up was 8.5y (0.2-36.6).
- 2,474 deaths (57% of cohort)-causes of death
  - 42% due to primary disease
  - 30% to graft versus host disease (GvHD)
  - 12% to infection
  - 5% to cardiopulmonary diseases
  - 3% to subsequent malignant neoplasm (SMN)
  - 8% to other causes.

F. Lennie Wong, et al. (Abstract #368)
Conditional Survival and Mortality Risks after Allogeneic Hematopoietic Cell Transplantation (alloHCT) in Patients Who Survived Varying Length of Time after AlloHCT (F. Lennie Wong, et al. (Abstract #368)

- Overall, the cohort was at a 24-fold (Standardized Mortality Ratio 24.1, 95%CI=23.1-25.0) risk of any death, compared to the general population.

- Risk of all-cause mortality was greatest in the first 5 years, although it remained significantly elevated in patients who survived 5 and 10y post alloHCT (SMR=3.7, 2.6, respectively, p<0.05)
  - Risk of death from pulmonary 31-fold
  - Risk death from subsequent malignant neoplasm 3 fold
  - Risk of death from cardiovascular complications was 3.5-fold.
In 10-year survivors of acute leukemia and chronic leukemia, all-cause mortality remained significantly higher compared to the general population (SMR > 1.8, p < 0.05).

Relapse mortality was significantly lower for patients who developed acute GvHD (HR = 0.78, 95% CI = 0.66-0.93).

Non disease related mortality increased
- With older age at HCT (HR = 1.02 per year, 95% CI = 1.01-1.03)
- For patients with acute GvHD (HR = 1.9, 95% CI = 1.6-2.2) and
- Exposure to Total Body Irradiation (TBI) (HR = 1.4, 95% CI = 1.2-1.8)
Conditional Survival Based on Years Survived Post HCT

For patients who had survived 6 mo, 1, 2, 5, 10y after alloHCT, the probability of survival in the next 5 years was 62%, 72%, 80%, 88% and 93%, respectively.

F. Lennie Wong, et al. (Abstract #368)
Conclusions:

- The projected 5-y survival rates for allogeneic transplant recipients improve conditional on time survived from alloHCT.

- 5-y survival is nearly 90% for those who have already survived 5 years.

- AlloHCT recipients surviving 10 years continue to have a significantly higher risk of mortality from pulmonary, cardiovascular disease and secondary malignancy compared to age matched general population.

- These data suggest clinical trials evaluating preventive and interventional strategies, unique to transplant patients, should be considered.
Transplants Safer - Relapse now is the primary cause of treatment failure after allogeneic HCT

- 10-60% of patients experience relapse post-HCT

- 2-year overall survival (OS) in adults with post-transplant relapse:
  - 16% in acute lymphoblastic leukemia (ALL)
  - 14% in acute myelogenous leukemia (AML)

Strategies for Treatment of Post-Transplant Relapse

• **Preemptive therapy upon detection of post transplant MRD**
  – Donor lymphocyte infusion
  – Abrupt withdrawal of CSA or tacro
  – Immuno-modulatory agents
    • 5-Azacytidine
    • IMIDs
    • Interferon alpha
    • Ipilimumab
    • PD-1 blockade

• **Targeted Therapies**
  – TKI inhibitors
  – Vaccination Strategies
  – Donor Leukemia specific T-cells-
  – CAR T-cells (CD19 CAR for relapsed ALL)
• Azacitidine (Aza) in combination with donor lymphocyte infusions (DLI), has proven to be a valuable treatment option for pts with relapse of MDS or AML after allo-SCT.
• Lenalidomide (Len) may further improve response rate and outcome due to its immunomodulatory and antileukemic properties
• Prospective, multicenter, single-arm phase-II trial evaluating the combination of Aza, Len and DLI in patients with MDS, AML or CMML who had relapsed after allo-SCT.
  • Cohort 1:
    • 8 cycles Aza (75 mg/m^2/d d1-7, every 28 days)
    • 3 DLI with increasing T cell dosages (0.5×10^6 - 1.5×10^7 cells/kg)
    • Lenalidomide 2.5 mg daily for 21 days of a 28-day cycle
  • Cohort 2:
    • 8 cycles Aza (75 mg/m^2/d d1-7, every 28 days)
    • 3 DLI with increasing T cell dosages (0.5×10^6 - 1.5×10^7 cells/kg)
    • Lenalidomide 5 mg daily for 21 days of a 28-day cycle
Treatment of MDS, AML and CMML Relapse after Allogeneic Blood Stem Cell Transplantation with Azacitidine, Lenalidomide and Donor Lymphocyte Infusions Results from the Second Interim Analysis of the Prospective Azalena-Trial (NCT02472691) (Schroeder et al: abstract 703)

Results:

- 24 pts, who had suffered from molecular (54%) or hematological (46%) relapse of MDS (58%), AML (38%) or CMML (4%) after median of 260 days (range, 61-2659) following allo-SCT
- Patients received
  - a median 5.5 cycles of Len per patient (range, 1 to 8)
  - a median of 7 courses Aza (range 2-8)
  - 71% received at least one DLI (median: 2, range: 1-12).
- No DLT was seen
- The increased Len dose did neither result in a higher frequency of dose reductions nor a higher number of AEs
- Overall response:
  - 68% (CR 58%, PR 10%).
  - CR rate higher in pts with molecular than in those with hematological relapse (67% vs. 43%)
  - All pts with CR remained in remission for a median of 183 days (range, 113-513)
  - 17% developed acute GvHD (overall grade II, II, III, III) and 21% ) chronic GvHD (mild n=2; moderate n=2; severe n=1).
  - Therapy-related CTC grade III/IV neutropenia (90%), thrombocytopenia (71%) or anemia (29%)

Schroeder et al: abstract 703
Tyrosine Kinase Inhibitors with or without Donor Lymphocyte Infusion Continue to Provide Long-Term Survival after Relapse of Chronic Myeloid Leukemia Following Hematopoietic Cell Transplantation

Methods and Results:

- 215 pts received either a TKI alone (n=128, 2) TKI with DLI (n=48) or 3) DLI without TKI (n=39).
- Patients that received a DLI alone compared to a TKI with DLI had inferior survival HR 2.28 (95% CI 1.23-4.24; p = 0.009).
- Those who received TKI alone had similar survival compared to those who received TKI with DLI (p=0.81).
- In a multivariate analysis, TKI with or without DLI remained significantly associated with superior survival compared to DLI alone (p=0.003).

Conclusions:

- TKI salvage therapy provides a significant survival advantage following relapse in patients with CML following HCT compared to DLI alone.

Schmidt S.A., et al abstract 704
A Phase I/Ib Study of Nivolumab for Relapsed Hematologic Malignancies after Allogeneic Hematopoietic Cell Transplantation (Davids et al : abstract 705)

**Background:**

- CTLA-4 blockade with ipilimumab was previously shown by this group to be feasible and active in pts with AML (Davids et al., N Eng J Med, 2016).
- Retrospective studies suggest anti-PD1 antibodies have activity in pts with relapsed lymphoid malignancies after alloHCT, though with substantial toxicity due to GVHD (Herbaux et al. and Haverkos et al., Blood, 2017).
- This is the first prospective clinical trial of PD1 blockade in pts with relapsed HM after alloHCT.

**Methods:**

- Phase I/Ib, multicenter, investigator-initiated, CTEP-sponsored study (CTEP 9204) were to determine MTD and evaluate safety of nivolumab (nivo) after allogeneic HCT.
- Secondary objectives were to assess efficacy and immunologic correlates.
- Pts with any hematological malignancies with relapse or persistent disease after alloHCT were eligible.
- Nivo was initially given to a 1 mg/kg with a planned escalation to a 3 mg/kg cohort or de-escalation to a 0.5 mg/kg cohort depending on toxicities.
- Nivo was dosed q2 wks until progression or unacceptable toxicity, and disease-specific response evaluations were q4 cycles.
A Phase I/IIb Study of Nivolumab for Relapsed Hematologic Malignancies after Allogeneic Hematopoietic Cell Transplantation (Davids et al : abstract 705)

Results:

• 28 pts (median age was 57 (range 27-76), with relapsed HM after alloHCT were treated.
  • Pts had the following diseases:
  • AML (n=11), MDS (n=7), Hodgkin lymphoma (HL, n=5), non-Hodgkin lymphoma (NHL, n=3), MPD and CLL (n=1 each).
  • 64% had progressed after at least 1 prior therapy for relapse post alloHCT.
  • The median time from alloHCT to study enrollment was 21 mo. (range 5.7-174 mo.).
• Cohort 1:
  • 6 pts were treated initially with nivo 1 mg/kg.
  • 2 immune-related deaths resulted in DLTs
    • one pt died with sepsis and fatal ARDS
    • one pt died with new anti-phospholipid antibodies and a fatal thrombotic cerebral vascular accident.
  • Other irAEs included gr3 pneumonitis and transaminitis (n=1 each). One pt had cGVHD (NIH mild). Response was observed in 3/6 pts, including 1 CR (PMBCL) and 2 PR (HL and CMML).
A Phase I/Ib Study of Nivolumab for Relapsed Hematologic Malignancies after Allogeneic Hematopoietic Cell Transplantation (Davids et al : abstract 705)

Results:

• Cohort 2 (n=8) de-escalated to nivo 0.5 mg/kg
• Generally well-tolerated, with no DLTs.
• A phase Ib expansion cohort then accrued a planned 15 more pts at 0.5 mg/kg.
  • Accrual was terminated after 14 pts were treated due to meeting the protocol-defined stopping rule of ≥4 DLTs in the first 15 pts in this cohort.
  • DLTs included
    • 2 cases of grade III acute GVHD (liver and gut) – both died from GVHD
    • 1 case grade III elevated bilirubin - survived
    • 1 case grade 3 transaminitis which did not recover to ≤gr1 within 4 wks.
    • Other toxicities included gr4 lipase elevation, gr3 rash, gr3 transaminitis, gr3 orthostatic hypotension, and gr2 seizure in a pt with a known seizure disorder (n=1 each).
  • Amongst the 2 pts treated at nivo 0.5 mg/kg, 45% had new onset or worsening of GVHD, including 1 with aGVHD only, 7 with cGVHD only (3 of whom had baseline cGVHD), and 2 with both acute and cGVHD.
A Phase I/Ib Study of Nivolumab for Relapsed Hematologic Malignancies after Allogeneic Hematopoietic Cell Transplantation (Davids et al: abstract 705)

Results and Conclusions:

- Shorter time from alloHCT was significantly associated with higher risk of developing GVHD (p=0.019).

- **16% overall response rate at the 0.5 mg/kg dose**
  - 1 pt with HL with CR and 1 pt each with HL and AML achieving PR.
  - 9 pts had stable disease for at least 1 response evaluation, and 7 pts had progressive disease as best response.

- Study wide, the overall response rate was only 24%

- The median number of cycles received was 3 (range 1-25), and 12/28 (43%) had at least 1 dose delay due to toxicity. With a median follow-up of 3.9 mo. (range 1.4-20.9 mo.), the 6 mo. PFS and OS were 39% and 61%, respectively.

- Post-transplant Nivo for relapse of heme malignancies was associated with significant toxicities including GVHD, even at the lower dose of nivo 0.5 mg/kg, leading to early closure due to toxicity.

- Modest anti-tumor activity was observed mainly in lymphoid malignancies known already to be responsive to anti-PD1 therapy.

- Given the more favorable safety and efficacy profile of anti-CTLA-4 therapy in other HM, future will studies focus on combining ipilimumab with novel partners to improve outcomes.
Thrombopoietin Receptor Agonists for Severe Thrombocytopenia after Allogeneic Stem Cell Transplantation: Experience of a Multicenter Study from the Grupo Español De Trasplante Hematopoyético (GETH)[ Bento L. et al: Abstract 200]

Honorable mention:

- 86 pts median age 53 who failed to achieve plts >50k post HCT
- Most had cord or haplo transplants
- 59% received eltrombopag (50-150) and 41% romiplostim- median treatment duration 2 months
- Median time to initiation of TPO mimetic was day 120 post HCT
- Results:
  - 72% achieved plts >50kt median 2 months
  - Only 2 % AEs
  - 81% stopped TPO mimetic and did not relapse