Can Transplantation improve survival rates for older patients with Higher risk MDS?

Professor Ghulam Mufti
I have the following financial relationships:

Advisory/working group: BMS/Celgene, Novartis
Contracted Research Paid to Department: BMS/Celgene, Novartis
Case History 1

70 year old man with MDS (IPSS-R, Score 4.5 Intermediate Risk)

Past medical History
1) Heavy smoker; Chronic obstructive pulmonary disease / Obstructive sleep apnoea-on CPAP
2) IHD discovered on screening CT angiogram 10 years ago, drug eluting stent- on daily Aspirin
3) total thyroidectomy (2 years ago for thyroid nodule) on L-thyroxin replacement
4) Type 2 DM on Metformin
5) Hyperlipidemia on Rosuvastatin 40 daily
6) Benign prostatic hypertrophy
7) Chronic gastritis on pantoprazole BID
8) Hepatitis B core antibody positive- on prophylactic tenofovir
9) Long History of Hidradenitis suppurativa requiring surgical intervention for recurrent gluteal lesions
10) Morbid obesity BMI >44
11) Fatty liver with increased resistant on Fibroscan
12) CT chest evidence of mild apical fibrosis suggestive of old TB
Case History 2

Presented 3 Years previously with slowly evolving thrombocytopenia
Mild macrocytosis, high ESR, Normal B12, folate, MMA, Negative Autoimmune screen
BM aspirate confirmed MDS with del(20q) (55%), U2AF1 mutation (8%), No excess blasts
Disease progressed after 3 years of stable course over preceding 3 months 11% blasts, few Auer rods
  IPSS-R, Score 4.5 Intermediate Risk
June 13th Venetoclax 100mg (+ posaconazole) x21 + Azacitidine x7(150mg)
    BM 7-8% Blasts
July 11th Venetoclax 100mg (+ posaconazole) x21 + Azacitidine x7(150mg) □
    BM morphological and cytogenetic CR
Case History 3

Aug 23rd PBSC Allo SCT from fully HLA and ABO matched sister using CD34: 8 x 106/kg (Day 0: 29th Aug 2021)
GVHD Prophylaxis: Tacrolimus and methotrexate (1,3,6)
Fludarabine 30mg/m2 (-6 to -2, Treosulfan 10gm/m2 (-4 to -2), SC Campath (20mg, 10mg)
Engrafted Day 10
Day 15 chimerism: Myeloid 82%, lymphoid 72%

Sep 27th Day 30 Post SCT:
BM in CR, no dysplasia in any of thr cell lineages ,del(20q)not detected on 500 cell FISH
PB Chimerism: Myeloid 100%, lymphoid 82%

Oct 24th Day 60 BM:
Normal marrow
Chimerism: Myeloid 100%, lymphoid 58%
withdrawal of FK-506, sequential chimerism and DLI
Case history question

- Would you have transplanted this 70 year-old gentleman with comorbidities?
  Yes or No
EBMT and IBMTR Allo-BMT Activity - 2019

**HCT Recipient Donor Type in the US by Age Group 2014-2019**

- Matched related donor
- Other relative
- URD-BM/PB
- URD-CB

**HCT activity in Europe 1990-2019**

main indication – allogeneic
HSCT Activity in Europe – 2009 to 2019

Myeloid malignancies
Total number = 48,512
10,518 transplants (98% allogenic)
AML – 7007 (HLA-A identical = 2027)
Haplo – 986
>2 Ag mismatch = 268
Unrelated = 3305
MDS/MPN = 2310

Passweg et al, BMT volume 56, 1651–1664 (2021)
## Impact of age on outcomes after HSCT?

<table>
<thead>
<tr>
<th></th>
<th>Lim et al EBMT 2010</th>
<th>McClune et al CIBMTR 2010</th>
<th>Alessandrino et al GITMO 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N, disease type</strong></td>
<td>1,333 MDS</td>
<td>1,080 total</td>
<td>357, MDS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>535 MDS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>545 AML (CR1)</td>
<td></td>
</tr>
<tr>
<td><strong>Age range, y (median)</strong></td>
<td>50–74 (56)</td>
<td>40–79 (AML, 12% &gt; 65y)</td>
<td>Trans dep: 21–72 (49)</td>
</tr>
<tr>
<td></td>
<td>34% &gt; 60y</td>
<td>40–78 (MDS, 10% &gt; 65y)</td>
<td>Trans indep: 18–65 (48)</td>
</tr>
<tr>
<td><strong>Conditioning, N, %</strong></td>
<td>500 (38%)</td>
<td>No SMC: All RIC/NMA</td>
<td>217 (61%)</td>
</tr>
<tr>
<td>SMC</td>
<td>833 (62%)</td>
<td></td>
<td>141 (39%)</td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td>4y OS 31% No diff. in OS between 50–60yrs Vs &gt;60 yrs RIC and advanced disease impacts RFS</td>
<td>No effect of age on NRM, DFS, OS or relapse Adverse cytogenetics impacts DFS negatively.</td>
<td>Transfusion dependency associated with inferior NRM and OS</td>
</tr>
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Comparison of Patient Age Groups in Transplantation for MDS

US Centres for Medicare and Medicaid Services
A CIBMTR Prospective Study (Dec 2010 – May 2014, 420 Centres Worldwide)

<table>
<thead>
<tr>
<th>Outcome details</th>
<th>55-64</th>
<th>65-79</th>
</tr>
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<tbody>
<tr>
<td>Age Group (yrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>592</td>
<td>688</td>
</tr>
<tr>
<td>Myeloablative (%)</td>
<td>288 (49%)</td>
<td>197 (29%)</td>
</tr>
<tr>
<td>RI Conditioning (%)</td>
<td>304 (51%)</td>
<td>491 (71%)</td>
</tr>
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<tr>
<th>GvHD</th>
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<tbody>
<tr>
<td>Acute (%)*</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>Chronic (%)*</td>
<td>44</td>
<td>47</td>
</tr>
<tr>
<td>Adjusted 3yrs OS (%)</td>
<td>42</td>
<td>37</td>
</tr>
<tr>
<td>RFS (%)</td>
<td>35</td>
<td>27*</td>
</tr>
</tbody>
</table>

Median Follow-up 47 Months (Data analysis Sept 2017)

*Fludarabine/Busulphan and T Cell depletion were associated with lower risk of GvHD

Blasts >11%: IPSSR high/very high; HCT-CI > 4= increased risk of relapse

Atallah et al, 2019 JAMA Oncol 6: 486-493
Role of Age and Co-morbidity Index in AlloHSCT in MDS (EBMT Study)

- 1245 cases (2003 – 2014), median age 59y (18 – 79)
  - HLA matched sibling – 34%
  - HLA matched unrelated – 44%
  - HLA mismatched unrelated – 18%
  - RIC = 744 (59.8%)
  - MAC = 501 (40.2%)
  - In vivo T depletion = 767 (67.6%)
- OS at 4y = 47%
- NRM at 4y = 32%
- HCT-CI = ≥3, Karnofsky = ≤80, increasing age all predictive of worse NRM

Carrie M et al, 2020; BBMT 451-457
Performance Status

- HCT – CI/Age (Sorror Score, 2005)
  - HCT >2, NRM 40%
  - HCT 0, NRM 14%
- European Bone Marrow Transplant Score
- PAM Score
- Frailty Index
- Geriatric Score
- Physician assessment
- Age
Transplantation considerations

**Disease factors**
- Disease (Low vs High risk)
- Cytogenetics
- Molecular markers: P53, DNMT3A, TET2, etc
- Depth of remission

**Conditioning**
- Donor type: (Sib/VUD/Haplo/Cord)
- Stem Cell source: (PB vs BM)
- Matching of donor
- Conditioning: (MA/NMA/RIC)
- T cell purging
- CMV status
- Donor age

**Post-transplant**
- GVHD
- Weaning IST
- Infections
- Monitoring: (MRD/Chimerism)
- Relapse: DLI (proph vs therapeutic)
- DNMTi/Chemotherapy
- Second transplant
- Adoptive immunotherapy
- Tumour vaccination

Is it ever possible to truly eradicate the malignant clone?
**Biological Assignment HSCT Trials in Older Patients With Intermediate-to-High Risk MDS**

<table>
<thead>
<tr>
<th></th>
<th>US Study</th>
<th>German Study</th>
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<tbody>
<tr>
<td><strong>Centres</strong></td>
<td>(34-Centres; 2014 – 18)</td>
<td>Multiple Centres (2011 – 2016)</td>
</tr>
<tr>
<td><strong>Number</strong></td>
<td>384 (50-75)</td>
<td>Number 108 (55-72)</td>
</tr>
<tr>
<td><strong>Donor</strong></td>
<td>260</td>
<td>81</td>
</tr>
<tr>
<td><strong>Matched related</strong></td>
<td>80</td>
<td>14</td>
</tr>
<tr>
<td><strong>Matched unrelated</strong></td>
<td>180</td>
<td>65</td>
</tr>
<tr>
<td><strong>Aza/Supportive</strong></td>
<td>124</td>
<td>27</td>
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<thead>
<tr>
<th></th>
<th>HSCT</th>
<th>No HSCT</th>
<th>HSCT</th>
<th>No HSCT</th>
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<tr>
<td><strong>Adjusted 3-year (%) survival</strong></td>
<td><strong>OS</strong></td>
<td>47.9</td>
<td>26.6 (P0.0001)</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td><strong>LFS</strong></td>
<td>35.8</td>
<td>20.6 (P.0003)</td>
<td>34</td>
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TRM 1yr: 19%
Only IPSSR affected OS and LFS

**SFGM-GFM Study: Prospective N: 162 (50-70 years)**
Donor: 112, No Donor: 50
4years OS: 37% vs 15% (P: 0.002)

Nyotaro N et al JCO 2021
Korger N et al JCO 2021, Gooley T Editorial JCO 2021
Robin M et al Leukaemia 2015
Retrospective EBMT study of 579 patients confirms validity of IPSS-R at HSCT irrespective of prior therapy

Median OS (months)
Very low: 23.6;  Low: 55;  Int: 19.7;  High: 13.5; Very high: 7.8

Multivariate Analysis Significant Factors
IPSS-R, graft source, age and prior treatment
Prognostic Systems and Treatment Eligibility

Classification and Personalized Prognostic Assessment on the Basis of Clinical and Genomic Features in Myelodysplastic Syndromes

ORIGINAL REPORTS | Hematologic Malignancy

Personalized Prediction Model to Risk Stratify Patients With Myelodysplastic Syndromes
Nazha, Aziz et al, J Clin Oncol. 2021 Aug 18
Overall survival according to remission status and percentage of marrow blasts

- Treated in CR1 (126 pts)
- RA-RARS, untreated (104 pts)
- RAEB-RAEB1-CMML, untreated (163 pts)
- Treated not in CR1 (130 pts)
### Bridge to Transplant in MDS Patients

<table>
<thead>
<tr>
<th>High/Very High/Intermediate Risk</th>
<th>Very Low/Low Risk</th>
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<tr>
<td>- 5-Azacytidine</td>
<td>Supportive Care ± HMA</td>
</tr>
<tr>
<td>- Decitabine</td>
<td></td>
</tr>
<tr>
<td>- Guadecitabine</td>
<td></td>
</tr>
<tr>
<td>- HMA (s/c</td>
<td>oral) + Venetoclax</td>
</tr>
<tr>
<td>- CP x351</td>
<td></td>
</tr>
<tr>
<td>- 3 + 7</td>
<td></td>
</tr>
<tr>
<td>- FLAG ± Venetoclax</td>
<td></td>
</tr>
<tr>
<td>- Clinical Trial Options</td>
<td></td>
</tr>
<tr>
<td>- ASTX 727 (ENHANCE 1&amp;2)</td>
<td></td>
</tr>
<tr>
<td>- Magrolimab + azacytidine</td>
<td></td>
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<tr>
<td>- Sabatolimab + Aza ± Venetoclax</td>
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Models for Overall Survival, Including Clinical and Genetic Variables and Effect of Conditioning Intensity

- N=1514
  - (pMDS = 1203, tMDS = 311)
  - <5% blasts = 646
  - MAC = 789
  - RIC = 582
  - NMA = 130
Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes

N=3324
Monoallelic = 33%
Multiple = 67%

Somatic Mutations Predict Poor Outcome in Patients With Myelodysplastic Syndrome After Hematopoietic Stem-Cell Transplantation

. Bejar R et al. JCO 2014;32:2691-2698
Choosing an older sibling versus a Volunteer Unrelated Donor?

**Conflicting Data**

EBMT data: improved survival in older MDS patient with use of young URD compared to MSD (Kroger et al 2012). NOT shown in other studies.

Early studies suggested a higher rate of GVHD with aged donors but this has not been consistent and conflicting data has emerged (Kolman et al 2001; Alousi et al 2013)

- Impaired B cell, T Cell and NK compartments; decreased diversity; chronic inflammation

- Stem cell Reserve decreases with ageing. Quality and Regenerative capacity of HSC obtained under GCSF mobilisation from an elderly donor is reduced
Role of donor clonal haematopoiesis in allogenic HSCT

1. 500 healthy, related HSCT donors (≥55yrs) targeted 66-gene panel sequencing
   - (1993 – 2017) Myeloid disease: 19.2 vs 6.3 (p<0.001)

2. 92 clonal mutations, median VAF of 5.9% in 80 (16.0%) donors
   - DNMT3a = 8%
   - TET2 = 2.2% (C→T)
   - ASXL1 = 1.4%

3. Alive patients median follow-up 3.3yr (0.1 - 20.6)
   - Higher cumulative incidence of cGVHD; hazard ratio (P=0.003)
   - Lower CIR/P (Univariate P =0.027; multivariate P=0.042)
   - No effect on non-relapse mortality and OS
   - 2 donor leukaemia's & lineage expansion of CHIP clone paralleled the fall in chimerism

CIBMTR (10,000 unrelated donor stem cell transplantation)
- 1999 – 2014 - younger donors are associated with a better transplant outcome

“Allogeneic HSCT from donors with CHIP seems safe and results in similar survival in the setting of older, related donors”

Frick et al JCO 201

Shaw et al Biol Blood Marrow Transplant. 2018
Thus there is no reason to exclude donors majority of cases with CH
Dose-Reduced Versus Standard Conditioning Followed by Allogeneic Stem-Cell Transplantation for Patients With Myelodysplastic Syndrome: A Prospective Randomized Phase III Study of the EBMT (RICMAC Trial).

129 patients with MDS and sAML

- Median age = 50
- Matched related (MAC/RIC) = 17/16
- Matched unrelated (MAC/RIC) = 36/38
- MM R/UR (MAC/RIC) = 11/11

- Randomly assigned 1:1
- OS at 2yrs = 76% (RIC), 63% (MAC)
- RFS at 2yrs = 62% (RIC), 58% (MAC)
- No difference in acute or chronic GVHD

RIC (n=65)
- Fludarabine: 150mg/m²
- Busulphan: 8mg/kg PO or 6.4mg/kg IV

MAC (n=64)
- Busulphan: 16mg/kg PO or 12.8mg/kg IV
- Cyclophosphamide: 120mg/kg

Kroger et al JCO 2017
Treosulfan vs Busulphan conditioning for AML/MDS

- Patient population – AML in 1st or consecutive complete remission or MDS blasts <20% in BM, Karnofsky index of <50%
- HSCT CI >2 and/or age >50y
- Total number of patients = 476 (age range = 18 -70y),
  - Busulfan conditioning = 240 (median follow-up = 17.4m), 2yr EFS = 50.4%, TRM = 28.2%
  - Treosulfan conditioning = 221 (median follow-up = 15.4m), 2yr EFS = 64%, TRM = 11.3%
- P<0.0001 for non-inferiority, P=0.0051 for superiority
- Patient population – AML in 1st or consecutive complete remission or MDS blasts <20% in BM, Karnofsky index of <50%
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  - Treosulfan conditioning = 221 (median follow-up = 15.4m), 2yr EFS = 64%, TRM = 11.3%
- P<0.0001 for non-inferiority, P=0.0051 for superiority

- Busulfan = 0.8mg/kg days -4 to -3
- Treosulfan = 10g/m² days -4 to -2
- Fludarabine = 30mg/m² days -6 to -2

Treosulfan or busulfan plus fludarabine as conditioning treatment before allogeneic haemopoietic stem cell transplantation for older patients with acute myeloid leukaemia or myelodysplastic syndrome (MC-FludT.14/L): a randomised, non-inferiority, phase 3 trial

Beelan et al, Volume 7, ISSUE 1, E28-E39, January 01, 2020
Allo HSCT in MDS using treosulfan based compared to other RIC and MAC regimes. A report of the chronic malignancies EBMT Working Party report

- N=1722
- FT = 367
- RIC = 687, MAC = 668
- Median age for FT = 59, RIC = 59, MAC = 51
- Median follow up = 64m (1 – 171)

- 5yr relapse rate = FT 25%, RIC 38%, MAC 25% p<0.001,
- NRM = FT 30%, RIC 27%, MAC 34%
- 5y OS = FT 50%, RIC 43%, MAC 43% p=0.03

Shimoni et al 12 September 2021 BJH
HLA-Mismatched/Cord Blood Donors in Patients with Myelodysplastic Syndrome: An EBMT Registry Analysis

CIBMTR analysis: n=176
Median age 56 (18-73) years
OS = 31% at 3yrs
NRM = 40% at 3yrs
Relapse – 32% at 3 yrs

Outcomes after cord blood transplant are limited by relatively high NRM

Gerds et al BBMT 2017

Robin et al BBMT 2018
Antilymphocyte Globulin for Prevention of Chronic Graft-versus-Host Disease

- N=168
- Median follow up = 24 months
- Chronic GVHD = 32.2% ATG group and 68.7 in non ATG group, P<0.001
- Chronic GVHD relapse free survival = 36.6 vs 16.8 p = 0.005
- Median age AML = 55y
- Conditioning TBI cycle, Busulfan cycle, TPI Etoposide
- AML 66% in ATG group and 76% in non-ATG group

Kroger et al, 2016 NEJM
Kings College Hospital Experience in 267 patients with MDS/AML transplanted with FBC conditioning
Confirms results of Deeg study in T-deplete setting
Relapse is the leading cause of treatment failure post HSCT

Prevention of relapse post HSCT now the most important challenge in AML/MDS
Mutation Clearance after Transplantation for Myelodysplastic Syndrome

- 86 of the 90 patients studies had a mutation
- Multivariate analysis showed that patients with a mutation and a variant allele frequency of at least 0.5% detected at day 30 had a higher risk of progression (P<0.001) and a lower 1-year rate of progression-free survival (P=0.002)
Potential Effects Following Exposure to Azacytidine

In-vivo effect of 5-azacytidine on the number of Tregs

Enhanced Expression of LAA by CD34+ cells at time of best response to 5’-azacytidine

68 patient with Int-2/HR Disease
Increase in “Treg like” cells which were non-functional and secreted more IL-17 compared to NR patients

Azacytidine for pre-emptive MRD+ in MDS/AML (RELAZA 2 trial)

• RELAZA – 2
• **Cohort 1** (2011 – 2015)
  • N=198 (AML: 172, MDS 26)
  • MRD + 60/198 (30%), 53/60: 5AZA 75mg x7
  • 31/53 (58%) relapse-free at 6/12 (P=<001), 6 courses.
  • MRD (-) = 88%
  • RFS @ 12months = 46%

• **Cohort 2**: 41/166: MRD + (CD 34 ,CD117 Chimerism)
  • 25/41 (61%) relapse-free at 6months (P=001)

Platzbecker et al
-Lancet ONC (2018)
-Blood 2020
Randomised study of oral Aza vs Placebo maintenance in AML/MDS after AlloHSCT (AMADEUS)

- 2 arm double blind phase III (2019 – 2021), oral Aza 200mg/14 days of 28 day cycle for 12 months
- Recruitment target n = 324
  - Transplant conditioning
  - Age
  - Donor type
- Completion 2024
Early Administration of Pre-emptive DLI correlates with durable AML/MDS Remission

- 64 patients
- Myeloid Malignancies
  - AML/MDS/MPN
- pDLI given if
  - Donor CD3 <50%
  - Falling donor CD3 >20% in one month
- Escalating Dose DLI
  - 6-8 Week Intervals

77% of patients achieved FDC or stable MDC after DLI
- 5yr OS was 91% in these patients

- OS at 5 years after pre-emptive DLI – 80%
- EFS at 5 years after pre-emptive DLI – 65%
- GVHD incidence – 31% (19% chronic extensive) after pre-emptive DLI
Post-Transplant/Relapse Strategies

Donor Lymphocyte Infusion
- Pre-emptive +/- DLI
- Therapeutic +/- DLI
- +/- Azacitidine +/- DLI
- Chemotherapy +/- DLI

Vaccination Strategies
- B7.1/IL2; WT1; etc

Check Point Inhibitors Therapy
- CTLA4; PD1; PDL1; etc

Neoantigens/Leukemia Associated Antigen Specific T cells

CAR123 Cellular Therapy

NK Mediated Cellular Therapy

Second Transplant

Antibody-based therapeutics (DARTs, BiTEs)
- CD33/CD3; MCLA-117/CD3; CD123/CD3

5-Azacytidine sc; CC486 (oral AzaC)
5-Aza + Venetoclax
5-Aza +/- Don’t eat me Inhibitors eg anti CD47
5-Aza + CPI’s eg TIM3 etc
5- Aza +/- Panabinostat
Case history question

- Would you have transplanted this 70 year-old gentleman with comorbidities?  
  Yes or No