Should every transplant eligible NDMM patient receive a transplant?.

YES

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Disclosures

• Research Support
  – CELGENE, SANOFI, Johnson & Johnson, Actinium, Millenium, AMGEN, TAKEDA

• Consulting
  – CELGENE, SANOFI, Johnson & Johnson, Actinium, Millenium, AMGEN
  – Kite (Gilead), Novartis, BMS, Jazz, Pfizer,

• I am a transplanter
What will it take to defend the YES position?

• Goal
  – Longest life with the best quality of life with the least burden of therapy
• To justify the YES position I must do one or all of the following
  • Demonstrable survival benefit of high dose melphalan consolidation.
  • Demonstrable progression free survival benefit of high dose melphalan.
  • Demonstrable cost-effective benefit of high dose melphalan consolidation.
  • Equivalent long term QOL.
Is high dose melphalan consolidation associated with a survival benefit?
**EMN02/HO95 MM study design**

### Induction
- **VCD** x 3-4 cycles + PBSC collection (1493 pts)

### Intensification
- **VMP** x 4 cycles
  - Bortezomib 1.3 mg/m²
  - d 1, 4, 8, 11, 22, 25, 29, 32, 42
- **Melphalan** 9 mg/m² d 1-4/42
- **Prednisone** 60 mg/m² d 1-4/42 (495 pts)

### Consolidation
- **VRD** x 2 cycles (449 pts)
- No consolidation (428 pts)

### Maintenance
- Lenalidomide (977 pts)

**Primary endpoints:**
- PFS from R1: ASCT vs VMP
- PFS from R2: VRD consolidation vs no consolidation

**Secondary endpoints:**
- PFS from R1: HDM-1 vs HDM-2
- Rates of response to ASCT or VMP
- OS from R1: ASCT vs VMP
- Toxicities with ASCT and VMP
Overall survival (extended follow-up: 75 months)

What will Morie say?

Old data

Who uses VMP today?

6% difference and what access to new agents did they have
Is there a PFS benefit for high dose melphalan consolidation in the era of modern MM induction?
Trial design

474 NDMM patients, transplant-eligible and younger than 65 years

4x KCd
K: 36 mg/m² d 1,2,8,9,15-16
C: 300 mg/m² d 1,8,15
d: 20 mg. d 1-2,8-9,15-16,22-23

4x KRd
K: 36 mg/m² d 1,2,8,9,15-16
R: 25 mg d 1-21
d: 20 mg. d 1-2,8-9,15-16,22-23

Single ASCT
Intensification with high-dose melphalan followed by autologous stem-cell reinfusion

4x KCd
K: 36 mg/m² d 1,2,8-9,15-16
C: 300 mg/m² d 1,8,15
d: 20 mg. d 1-2,8-9,15-16,22-23

4x KRd
K: 36 mg/m² d 1,2,8,9,15-16
R: 25 mg d 1-21
d: 20 mg. d 1-2,8-9,15-16,22-23

R
R: 10 mg days 1-21, until progression or intolerance

R2
1:1

KR
K: 36 mg/m² d 1, 2, 15, 16 up to 2 years
R: 10 mg days 1-21, until progression or intolerance

^20 mg/m² on days 1-2, cycle 1 only. *Carfilzomib 70 mg/m² days 1, 15 every 28 days up to 2 years for patients that have started the maintenance treatment from 6 months before the approval of Amendment 5.0 onwards. NDMM, newly diagnosed multiple myeloma; R1, first randomization (induction/consolidation treatment); R2, second randomization (maintenance treatment); IQR, interquartile range K, carfilzomib; C, cyclophosphamide; R, lenalidomide; d, dexamethasone; d, days; ASCT, autologous stem-cell transplantation.
Progression-free survival: Random 1

Median follow-up from Random 1: 45 months (40-49 months)

Rate of sustained MRD MCF $10^{-5}$

- Sustained MRD
  - KRD ASCT: 68%
  - KRd12: 54%
  - KCd ASCT: 45%

- P = 0.02
- P < 0.001

Progression-free survival

- KRd ASCT vs. KCd ASCT: HR 0.53, 95% CI 0.37-0.77, p < 0.001
- KRd ASCT vs. KRd12: HR 0.64, 95% CI 0.44-0.94, p = 0.023
- KRd12 vs. KCd ASCT: HR 0.82, 95% CI 0.59-1.16, p = 0.262

Random 1, first randomization (induction/consolidation treatment); ASCT, autologous stem-cell transplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd, induction-ASCT-KCd consolidation; KRd ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; p, p-value; HR, hazard ratio; CI, confidence interval; MRD, minimal residual disease; MFC, multiparameter flow cytometry; 3-year PFS reported in the figure.
IFM 2009 Study design

700 patients randomized stratified on ISS and FISH

Arm A – RVD alone
- 3 RVD
- PBSC collection (cyclophosphamide 3g/m² and GCSF 10 μg/kg/d)
- 5 RVD
- Lenalidomide maintenance 13 cycles (10-15 mg/d)

Arm B - Transplantation
- 3 RVD
- HD Melphalan 200 mg/m² + ASCT
- 2 RVD

RVd 21d cycles
- Lenalidomide 25 mg/d: D1-D14
- Bortezomib 1.3 mg/m² D1, D4, D8, D11
- Dexamethasone 20 mg/d: D1, D2, D4, D5, D8, D9, D11, D12

Primary endpoint = PFS
Secondary endpoints
- ORR, MRD
- TTP
- OS
- Toxicity

M Attal et al, N Engl J Med 2017
Updated PFS (primary endpoint)

Median follow up  89.8 months

HR (95CI)  0.70 [0.59;0.83]

Median PFS  47.3 months (Transplantation, arm B)

Median PFS  35 months (RVD alone, arm A)

30% reduction in the risk of progression or death in patients receiving transplant
Median follow up: 89.8 months

More than 60% of the patients in the two arms are alive after 8 years of follow-up.
Subgroup analyses

Transplant is superior to VRD alone, even in patients who achieved undetectable MRD at $10^{-6}$

Median follow up: 89.8 months

MRD negativity rate

- RVD alone: 20.4%
- Transplant: 29.79%

p 0.01
Is there a cost-effective benefit of high dose melphalan consolidation?
What would Morie say?

  - "The Consumer Price Index adjusted 2012 costs of eASCT and dASCT were $249,236 and $262,610, respectively. eASCT cohort had a benefit of 1.96 quality-adjusted life years (QALYs), 0.23 QALYs more than dASCT, implying that eASCT is preferred (dominant) over dASCT."

  - "Twenty-four publications were included in the systematic review and summarized according to treatment regimen and line. For first-line treatment, transplant was the most cost-effective option for transplant-eligible MM patients [the incremental cost-effectiveness ratio (ICER) was $4053-€45,460 per quality-adjusted life-year (QALY) gained, and $3848-$72,852 per life-year gained (LYG)..."
Can we make high dose melphalan better?
Higher Melphalan AUC Predicts Time to Progression, Overall Survival, and Toxicity

- Melphalan median AUC 12.85 mg/L.h
- Mucositis >= Grade 3
  - 12% clinical, 20% functional
  - Multivariate analysis Melphalan AUC (continuous), HR 1.2, p = 0.004

*Shaw BBMT 2012;18(2):S207
PFS by AUC (n=25)
How about QOL?
Incidence of Moderate to Severe Symptoms Post Auto HCT for MM. Anderson et al. BMT
Can we make high dose melphalan better tolerated?
Interventions

- Nausea/Vomiting
  - 5HT antagonists
- Pain
  - Opiates
- Cytopenias
  - Filgrastim
  - Erythropoietin
- Diarrhea
  - Octreotide
- Mucositis
  - Opiates
  - Palifermin
- Fatigue

**Isolated treatment of symptoms**
No understanding of the effects of control of one symptom over another

Efficacy of interventions generally measured only in one dimension
True

The Sham Acupuncture group had greater than five times odds of increasing pain medication use from baseline. Deng G et al. Pain Medicine 2020
IL6 is the main cytokine driver of symptoms after auto HCT

Wang et al, J Clin Oncol

Cytokine blockade as a potential strategy to reduce symptom burden
Phase II Trial of IL6 Blockade
### Siltuximab Treated Patients (N=28)

<table>
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<tr>
<th>Question Short</th>
<th>Day 10/Day 7</th>
<th>Day 17</th>
<th>Day 30</th>
<th>Day 11</th>
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### Historical Control (N=10)

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<th>Day 11+</th>
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**Symptom Interference (0-10)**

- **Score**: 0.00 to 10.00
- **Avg. Score**: 0.000 to 9.111
In Summary

- High dose melphalan with autologous stem cell support as consolidation of initial therapy has been shown in multiple randomized trial to be associated with a significant PFS benefit.
- With long term follow up that PFS benefit can translate into a OS benefit and definitely a reduction in the burden of therapy and the need for new treatments.
- A priori, we cant identify who could benefit from HDM and thus all transplant eligible patients should receive it.
- Even patients with MRD negativity benefit from HDM and thus depth of response to induction should NOT be considered a reason not to proceed.
- POSSIBLE EXCEPTIONS
  - Low risk Stage 1 disease in a older patient (75 or older) MRD negative to induction.
  - Patients beyond one year of induction
• Dose intense therapy was one of the first strategies developed to overcome drug resistance.
• Dose intense therapy can overcome multiple resistance pathways
• High dose melphalan is associated with less than 1% NRM
• 2nd primary malignancies an issue that we need to better understand and address
• Mechanisms of resistance to high dose therapy need to be investigated with the same enthusiasm that we investigate mechanisms of resistance to other immune therapies. Suboptimal dosing could be one of them and is likely the easiest to address
• Most of the newer therapies could enhance outcomes after high dose therapy and should be complementary and not mutually exclusive
• **REMEMBER TO REGISTER TO THE 5th INTERNATIONAL WORKSHOP ON THE BIOLOGY, PREVENTION AND TREATMENT OF RELAPSE AFTER HEMATOPOIETIC CELL TRANSPLANTATION AND CELLULAR THERAPIES HSCT²**
• **Join Online or Live in New York City for HSCT² October 8-9, 2021 Sheraton Times Square New York City,**
• **Register now LINK https://www.relapse-after-hsct.com/**
Questions?
giralts@mskcc.org
7135045082