Post Transplant Maintenance- for everyone?

NO – Because of limited survival data, not all patients require maintenance

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Scottsdale, Arizona
Rochester, Minnesota
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Disclosures

• NONE
Objectives

1. Review the importance of the heterogeneity of myeloma and its impact on therapy selection
2. Appreciate that recent evidence for maintenance as prolonging PFS in SOME patients is not an overall survival advantage
3. Discuss the reality that PFS is NOT survival
4. Emphasize what is at stake when we globally apply maintenance therapy to patients with myeloma
5. Give practical advice as to when to consider maintenance therapy

What are the Characteristics of a Good Maintenance Drug?

1. Better overall survival
2. Good tolerability / safety profile
3. Better progression free survival AND better QOL
Maintenance treatment in multiple myeloma.
A HISTORY LESSON.

• Chemotherapy: No: SWOG,1 Alexanian,2 and Belch3
• Corticosteroids: Yes: survival and duration of response;6
  No: no survival improvement7, 8
• Interferon: Yes: Mandelli;4 No: Meta-analysis—modest increase in PFS with only minimal to no survival benefit5
• Thalidomide: Yes/No: 1 of 3 non-ASCT positive; 2.5 of 7 ASCT trials positive
• Lenalidomide: Yes/No: Too early; 1 positive; 1 negative
• Bortezomib: No data to isolate effect


<table>
<thead>
<tr>
<th>Maintenance after ASCT with thal</th>
<th>Initial dose, mg</th>
<th>Maintenance versus no maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barlogie1 Abn Cyto</td>
<td>668</td>
<td>83% received salvage thalidomide→</td>
</tr>
<tr>
<td>Attal2</td>
<td>597</td>
<td>62% received salvage thalidomide→</td>
</tr>
<tr>
<td>Spencer3</td>
<td>243</td>
<td>54% received salvage thalidomide→</td>
</tr>
<tr>
<td>Morgan4</td>
<td>492</td>
<td>100 38 30 vs 23 m</td>
</tr>
<tr>
<td>Stewart5</td>
<td>332 (+pred)</td>
<td>200 48 28 vs 17 m</td>
</tr>
<tr>
<td>Lokhorst6</td>
<td>536 (vs IFN)</td>
<td>50 52 34 vs 25 m</td>
</tr>
<tr>
<td>Krishnan7</td>
<td>366 (+dex)</td>
<td>200 36 3-yr 49 v 43%</td>
</tr>
</tbody>
</table>

* CR rate only. † Risk of death 1.8x higher in patients with adverse cytogenetics if thal maintenance

Which is the Better Strategy?

Maintenance drug X

versus

Observation

Relapse regimens minus maintenance drug X

Relapse regimens including maintenance drug X

1. Subsequent therapy differently effective in the randomly assigned treatment arms
2. Subsequent therapy equally effective in the randomly assigned treatment arms
3. Cross-over to experimental therapy

In this situation, we would again argue that the observed, possibly attenuated, OS difference is the appropriate measure of clinical benefit because it properly reflects the clinical reality of available subsequent treatments for the experimental and standard treatments.
Thalidomide Maintenance after ASCT
IFM 99-02

Patients
<65 yr old
Neither or either
β2M ≤ 3, del 13
↓
VAD
3–4 cycles
↓
Melphalan,
140 mg/m²,
ASCT
↓
Melphalan,
200 mg/m²
ASCT

No maintenance therapy
n=197
Randomized if no progression
Pamidronate, 90 mg/mo
n=195

Pamidronate, 90 mg/mo
Thalidomide, 100 mg/day
n=201

OS from Diagnosis

PFS from Diagnosis

Barlogie JCO (2010);28:1209-14, supplementary material
HOVON 50 Stage II/III MM, < 66 years

267 pts

VAD (3x)

IV push

88%

CAD + G-CSF

Cyclo/adria/dex

HLA-id Sib

RIC

N=109

HDM 1-2x

200mg/m²

23%

82%

α-IFN

Thrice/weekly

34%

HOVON 54

200mg/m²

200%

23%

Thalidomide

50 mg/daily

58%

Lokhorst Blood (2010); 115:1113-1120

HOVON 50

Best response on protocol

VAD+IFN

TAD+Thal

≥ PR

79 %

88%

0.005

≥ VGPR

54 %

60%

0.005

≥ CR

23 %

31%

0.04

EFS with censoring at RIC allo-SCT

Treatment arm

Cumulative percentage

0 25 50 75 100

0 25 50 75 100

At risk:

A:noThal  267  138  84  44  15  3

B:+Thal  269  163  123  74  34  9

Logrank P<.001

At risk:

A:noThal  267  227  204  151  65  20

B:+Thal  269  233  201  148  80  24

Logrank P=.96

Median fu is 52 months

Lokhorst Blood (2010); 115:1113-1120
Characteristics of a Good Maintenance Drug

**Thal**

1. Better overall survival +/-

2. Good tolerability / safety profile No

3. Better progression free survival AND better QOL No

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Lenalidomide
**IFM 2005-02: Study design**

**Phase III randomized, placebo-controlled trial**

N= 614 patients, from 78 centers, enrolled between 7/2006 and 8/2008

- **Patients < 65 years, with non-progressive disease, ≤ 6 months after ASCT in first line**

- **Randomization:** stratified according to Beta-2m, del13, VGPR

<table>
<thead>
<tr>
<th>Consolidation: Lenalidomide alone</th>
<th>25 mg/day p.o. days 1-21 of every 28 days for 2 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arm A=</strong></td>
<td><strong>Placebo</strong> (N=307) until relapse</td>
</tr>
<tr>
<td><strong>Arm B=</strong></td>
<td><strong>Lenalidomide</strong> (N=307) 10-15 mg/d until relapse</td>
</tr>
</tbody>
</table>

**Primary end-point:** PFS

**Secondary end-points:** CR rate, TTP, OS, feasibility of long-term lenalidomide...


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**IFM 2005-02: Phase III randomized, placebo-controlled trial-Len Maintenance post-ASCT**

**Median follow up:** 34 m post random, 44 m post diagnosis

- **PFS**
  - Len (n =307) ~42 mo
  - Placebo (n = 307) ~24 mo
  - P < 10^-8

- **OS**
  - ~88% at 3 years
  - P=0.57

IFM 2005-02: Second Malignancies
According to time post randomization (4/2011)

Cumulative incidence: Placebo = 6.9 for 1000 patient-year
Len = 24.1 for 1000 patient-year (p=0.004)

Phase III Intergroup Study of Lenalidomide Vs Placebo Maintenance
Therapy Following Single Autologous Hematopoietic Stem Cell
Transplantation for MM: CALGB 100104

Patient stratification based on diagnostic /β-2M and thalidomide and lenalidomide therapy during induction

Median TTP: 39.6 mo (original report 42 mo)

Median TTP: 21.9 mo

13 deaths in the lenalidomide arm
24 deaths in the placebo arm

P < 0.0001

P = 0.05

ITT Analysis with a Median Follow-up from transplant of 18 months


Median TTP: 48 mo

Median TTP: 30.9 mo

23 deaths in lenalidomide arm
39 deaths in placebo arm

P < 0.0001

P = 0.018

ITT Analysis with a Median Follow-up from transplant of 28 months.


3 year OS: 87%

3 year OS: 82%
Critiques of CALGB Study

- CALGB powered to find a prolongation of TTP from 24 → 33.6 months (9.6 months)
  - Why only 9.6 months if we know that PFS of Len-Dex new diagnosis/no transplant is 25 months and at relapse is 12 months?
- Potentially biased toward lenalidomide responders
- Once cross-over occurred at 18 months for a TTP of 42 vs 22 months, data very difficult to interpret
  - Since median PFS of ASCT is 22 months, patients started on lenalidomide at inadequate doses right around their relapse.
- Incomplete and potentially imbalanced follow-up

Comparing Len Induction to Len Maintenance

<table>
<thead>
<tr>
<th>Study</th>
<th>Arm</th>
<th>Median PFS/TTP</th>
<th>2 yr PFS/TTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAINTENANCE STUDIES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFM¹</td>
<td>Placebo</td>
<td>24 mo</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Len</td>
<td>42 mo</td>
<td>70%</td>
</tr>
<tr>
<td>CALGB²</td>
<td>Placebo</td>
<td>22 mo</td>
<td>~45%</td>
</tr>
<tr>
<td></td>
<td>Len</td>
<td>42 mo</td>
<td>~72%</td>
</tr>
<tr>
<td>LEN INDUCTION STUDIES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mayo³</td>
<td>No SCT</td>
<td>32 mo</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td>SCT</td>
<td>NR</td>
<td>83%</td>
</tr>
<tr>
<td>ECOG⁴</td>
<td>Late SCT</td>
<td>36 mo</td>
<td>58%</td>
</tr>
<tr>
<td></td>
<td>SCT</td>
<td>NR</td>
<td>75%</td>
</tr>
</tbody>
</table>

¹ Attal ASH 2010  
² McCarthy ASH 2010  
³ Lacy Mayo Proc 2009  
⁴ Siegel ASH 2010
Adverse Events during Lenalidomide Maintenance

<table>
<thead>
<tr>
<th></th>
<th>Gr 3, %</th>
<th>Gr 4, %</th>
<th>Gr 5, %</th>
<th>Gr 3-5, %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heme Tox</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>31</td>
<td>14</td>
<td>0</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>7</td>
<td>4</td>
<td>0</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Non-Hem Tox</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>29</td>
<td>3</td>
<td>1</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>19</td>
<td>4</td>
<td>2</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

Febrile neutropenia, gr 3-5: 6% vs 2%, p=0.03
All other infections, gr 3-5: 16% vs 5%, p=0.001

What about QOL? What about grade 1-2 toxicities?

“Excluding progressive disease, 12% on Lenalidomide and 1% on placebo came off therapy due to AEs

and

20% on Lenalidomide 7% on placebo came off therapy for other reasons”
Secondary Malignancies with Maintenance Lenalidomide

<table>
<thead>
<tr>
<th></th>
<th>IFM</th>
<th>CALGB</th>
<th>MM015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Len 17/299 5.5%</td>
<td>Len 15/231 6.5%</td>
<td>MPR 11/355 3.1%</td>
</tr>
<tr>
<td>Placebo</td>
<td>3/292 1.0%</td>
<td>Placebo 6/229 2.6%</td>
<td>Placebo 2/154 1.3%</td>
</tr>
</tbody>
</table>

Not dramatic, but bears consideration...

CALGB Second Cancers

<table>
<thead>
<tr>
<th></th>
<th>Len 8 / 231  ALL (1), HL (1), AML (5), MDS (1)</th>
<th>Placebo 0 / 229</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heme malignancies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid tumors</td>
<td>10 / 231  GI (2), Breast (2), Gyn (2), CNS (1), Prostate (1), Thyroid (1), Melanoma (1)</td>
<td>4 / 229 Carcinoid (1), Sarcoma (1), Melanoma (2)</td>
</tr>
</tbody>
</table>
Characteristics of a Good Maintenance Drug

1. Better overall survival

2. Good tolerability / safety profile

3. Better progression free survival AND better QOL

Best Regimen for Maintenance?

• **IFN:** 4 month OS benefit in non-HSCT; no benefit post HSCT

• **Corticosteroid:** 1 positive in steroid responsive; No benefit in another

• **Thalidomide:** 1 of 3 non-ASCT positive; 2.5 of 7 ASCT trials positive

• **Lenalidomide:** Too early; 1 positive; 1 negative

• **Bortezomib:** No data to isolate effect

Observation: Still standard of care
Conclusions

- First do no harm
- Consider QOL and AEs
- PFS inadequate endpoint for maintenance study placebo vs active drug design
- Len maintenance not yet proved to be superior to salvage Len
- One immature, (weakly) positive study does not change practice esp. if 2nd more mature trial negative
- Don’t forget COST!

Dollar Cost of Regimens (BSA 2 m²)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>per 28 days</th>
<th>per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. VRD</td>
<td>$23,000</td>
<td>(276K)</td>
</tr>
<tr>
<td>2. VTD</td>
<td>$22,000</td>
<td>(264K)</td>
</tr>
<tr>
<td>3. PAD</td>
<td>$14,400*</td>
<td>(173K)</td>
</tr>
<tr>
<td>4. VD</td>
<td>$13,800</td>
<td>(166K)</td>
</tr>
<tr>
<td>5. CyBorD (weekly)</td>
<td>$ 9,200</td>
<td>(110K)</td>
</tr>
<tr>
<td>6. Rd</td>
<td>$ 9,000</td>
<td>(108K)</td>
</tr>
<tr>
<td>7. TD</td>
<td>$ 8,200</td>
<td>( 98K)</td>
</tr>
</tbody>
</table>

*add $4000 if Doxil
Do I use Maintenance at All?

• Yes, when expected PFS after ASCT is limited due to high risk disease
  • Usual 20-24 months not in play
  • Willing to “buy” risks of ongoing therapy

Is this just Dr. Joe?

• IMWG statement on maintenance therapy
mSMART – Off-Study
Transplant Eligible

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Intermediate Risk</th>
<th>Standard Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRD x 4</td>
<td>Induction with CyBorD</td>
<td>4 cycles of Rd or CyBorD</td>
</tr>
<tr>
<td>ASCT, especially if not in CR</td>
<td>Autologous stem cell transplant (ASCT)</td>
<td>Collect Stem Cells(^b)</td>
</tr>
<tr>
<td>VRD maintenance for minimum of 1 year</td>
<td>Bortezomib based consolidation for minimum of 1 year</td>
<td>Autologous stem cell transplant (ASCT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continue Rd(^c)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider Lenalidomide maintenance(^*)</td>
</tr>
</tbody>
</table>

\(^a\) Bortezomib containing regimens preferred in renal failure or if rapid response needed
\(^b\) If age >65 or > 4 cycles of Rd Consider G-CSF plus cytoxan or plerixafor
\(^c\) Continuing Rd is option for patients responding to Rd and with low toxicities; Dex is usually discontinued after first year
\(^*\) Len maintenance may be less helpful for patients who have received len induction

Concluding thought…

• As myeloma becomes more “chronic” we must consider the long term strategy, not just short term PFS

• Maintenance therapy will lead to unnecessary therapy for many now, and much more complex relapses later

• Learn from the rituximab story of ASH 2011…