Approach to the Treatment of Newly Diagnosed Multiple Myeloma

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No conflicts to disclose
# NCCN Guidelines

## Preferred Regimens

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Therapy for Transplant Candidates</td>
<td>Bortezomib/dexamethasone (category 1)</td>
</tr>
<tr>
<td>(Assess for response after 2 cycles)</td>
<td>Bortezomib/cyclophosphamide/dexamethasone</td>
</tr>
<tr>
<td></td>
<td>Bortezomib/doxorubicin/dexamethasone (category 1)</td>
</tr>
<tr>
<td></td>
<td>Bortezomib/lenalidomide/dexamethasone (category 1)</td>
</tr>
<tr>
<td></td>
<td>Bortezomib/thalidomide/dexamethasone (category 1)</td>
</tr>
<tr>
<td></td>
<td>Lenalidomide/dexamethasone (category 1)</td>
</tr>
<tr>
<td>Primary Therapy for Non-Transplant Candidates</td>
<td>Bortezomib/dexamethasone</td>
</tr>
<tr>
<td>(Assess for response after 2 cycles)</td>
<td>Lenalidomide/low-dose dexamethasone (category 1)</td>
</tr>
<tr>
<td></td>
<td>Melphalan/prednisone/bortezomib (MPB) (category 1)</td>
</tr>
<tr>
<td></td>
<td>Melphalan/prednisone/lenalidomide (MPL) (category 1)</td>
</tr>
<tr>
<td></td>
<td>Melphalan/prednisone/thalidomide (MPT) (category 1)</td>
</tr>
</tbody>
</table>

## Other Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carfilzomib/lenalidomide/dexamethasone (category 2B)</td>
</tr>
<tr>
<td>Dexamethasone (category 2B)</td>
</tr>
<tr>
<td>Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B)</td>
</tr>
<tr>
<td>Thalidomide/dexamethasone (category 2B)</td>
</tr>
<tr>
<td>Dexamethasone (category 2B)</td>
</tr>
<tr>
<td>Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B)</td>
</tr>
<tr>
<td>Melphalan/prednisone (MP)</td>
</tr>
<tr>
<td>Thalidomide/dexamethasone (category 2B)</td>
</tr>
<tr>
<td>Vincristine/doxorubicin/dexamethasone (VAD) (category 2B)</td>
</tr>
</tbody>
</table>

## 7 regimens “2A” for transplant Eligible

NCCN. 2013
Myeloma Treatment Strategies

Aggressive therapy

- Triplet or quadruplet induction
- Early transplant
- Lenalidomide maintenance

“Cure” Approach
Emphasis is on CR

Sequential Therapy

- Doublet or “mild” triplet induction
- Early or late transplant
- Optional Maintenance

“Control” Approach
Emphasis is on QOL
Principles of Risk Adapted Therapy

“Avoid *unproven* therapies in good-risk patients”

- Toxicity
- QOL
- Cost
- Patient wishes and tolerance to risk
# PROGNOSIS IN MYELOMA

<table>
<thead>
<tr>
<th>Prognostic determinant</th>
<th>Standard risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Host factors</td>
<td>ECOG performance status 0-2</td>
<td>ECOG performance status 3 or 4</td>
</tr>
<tr>
<td></td>
<td>Normal renal function</td>
<td>Renal failure (serum creatinine ≥ 2.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Advanced age</td>
</tr>
<tr>
<td>Tumor burden</td>
<td>Durie-Salmon stage I, II</td>
<td>Durie-Salmon stage III</td>
</tr>
<tr>
<td>Tumor biology (disease aggressiveness)</td>
<td>Hyperdiploidy t(11;14) t(6;14)</td>
<td>t(4;14)* t(14;16) t(14;20) 17p-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High LDH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High plasma cell proliferative rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High-risk signature on gene-expression profiling</td>
</tr>
</tbody>
</table>

TUMOR BURDEN (STAGE)
HOST FACTORS

- Age, performance status, comorbidities
- Renal Failure
Myeloma Risk-Stratification

**High-Risk**
- Del 17p (p53)
- t(14;16) (C-MAF)
- t(14;20) (MAF-B)
- High-risk GEP (gene expression profile)

*Median survival <3 years*

**Intermediate-Risk**
- t(4;14) (FGFR3/MMSET)

*Median survival 3-5 years*

**Standard-Risk**
- All others including:
  - Hyperdiploid (trisomies)
  - t(11;14) (CCND1)
  - t(6;14) (CCND3)

*Median survival 6-7 years*

*Presence of trisomies converts high risk into standard risk*
Myeloma Risk-Stratification

High-Risk*
- Del 17p
- t(14;16)
- t(14;20)
- GEP defined high-risk

Intermediate-Risk*
- t(4;14)

Standard-Risk
- Hyperdiploid
- t(11;14)
- t(6;14)

*Presence of trisomies ameliorates high risk

CR appears critical
Bortezomib Critical
Excellent Outcome regardless of how you treat

Outcome similar to standard risk if treated with bortezomib
CR is critical in patients with high-risk myeloma

Low-Risk MM (87%)

High-Risk MM (13%)

Doublet-Regimens

Thal-Dex (TD)  Len-Dex (RD)  Bortez-Dex (VD)

PFS better than Dex/VAD

Harousseau J et al. JCO 2010;28:4621-4629
TRANSPLANT ELIGIBLE
Can 3 or more drug regimens provide additional benefit?

**Doublets**
- TD
- RD
- VD

**Triplets**
- VTD
- VRD
- PAD
- VCD

*Other triplets: Anthracycline containing regimens; Carfilzomib-Rd, MLN9708-Rd*
VTD versus VD
Progression-free survival.


\[ p = 0.22 \]
VTD vs TD
Progression free survival

Cavo et al. Lancet 2010
HR, 0.76 [CI: 0.46-1.27]  
p=0.3071

Probability at 3 yrs (%)  
87 84  
p=0.3042

Cavo ASH 2010
PAD vs VAD: PFS and Overall Survival

Sonneveld P et al. JCO 2012;30:2946-2955

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PAD vs VAD: OS according to del(17p)

Sonneveld P et al. JCO 2012;30:2946-2955
VRD

- 66 evaluable pts
  - CR 29%
  - nCR 11%
  - VGPR 27%

PR (33%)

- Overall response rate: 100%

Richardson PG. Blood 2010;116:679-686
### VCD (CyBorD) Table

| Response, %        | VCD  
|--------------------|------
| CR/nCR             | 41%  
| ≥ VGPR             | 60%  
| ORR (≥ PR)         | 90%  

*Mayo Clinic*

Reeder C. Blood 2010
Can 4 or more drug regimens provide additional benefit?

<table>
<thead>
<tr>
<th>Doublets</th>
<th>Triplets</th>
<th>Quadruplets</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD</td>
<td>VTD</td>
<td>VDCR</td>
</tr>
<tr>
<td>RD</td>
<td>VRD</td>
<td>CTVD</td>
</tr>
<tr>
<td>VD</td>
<td>VCD</td>
<td>CDDV</td>
</tr>
<tr>
<td></td>
<td>PAD</td>
<td></td>
</tr>
</tbody>
</table>
## EVOLUTION RANDOMIZED TRIAL
**VRD vs VCD vs VDCR**

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>VDCR (n = 48)</th>
<th>VRD (n = 42)</th>
<th>VCD (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>25%</td>
<td>24%</td>
<td>30%</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>58%</td>
<td>51%</td>
<td>44%</td>
</tr>
<tr>
<td>ORR (≥ PR)</td>
<td>88%</td>
<td>85%</td>
<td>82%</td>
</tr>
</tbody>
</table>

How do we choose?

<table>
<thead>
<tr>
<th>Doublets</th>
<th>Triplets</th>
</tr>
</thead>
<tbody>
<tr>
<td>• RD</td>
<td>• VRD</td>
</tr>
<tr>
<td></td>
<td>• VCD</td>
</tr>
</tbody>
</table>
Dose of Dexamethasone

Doublets

• Rd

• Once weekly bortezomib

Triplets

• VRd

• VCd

Transplant Eligible-Off Study

**High Risk**
- 4 cycles of VRd
- ASCT

**Intermediate Risk**
- 4 cycles of VCd
- ASCT

**Standard Risk**
- 4 cycles of Rd or VCd
- ASCT

Additional information:
- VCd or VTd
TRANSPLANT INELIGIBLE
MP-plus Regimens

**MPT**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>O/N</th>
<th>Overall survival time (months) median (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP</td>
<td>128/196</td>
<td>33.2 (3.2)</td>
</tr>
<tr>
<td>MPT</td>
<td>62/125</td>
<td>51.6 (4.5)</td>
</tr>
<tr>
<td>MEL100</td>
<td>78/126</td>
<td>38.3 (2.7)</td>
</tr>
</tbody>
</table>

**VMP**

Surviving Patients (%)

- Bortezomib
- Control

$p=0.008$

Facon T. Lancet 2007;370:1209
## VMPT vs VMP Overall Survival

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>VMPT- VT</th>
<th>VMP</th>
<th>5-years OS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.75</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.00</td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

HR 0.70 (95% CI, 0.52-0.92, P < 0.01)

Palumbo A. ASH 2012
## Options in Transplant Ineligible Patients

### Non-melphalan based
- Rd
- VCd
- VRd

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>TTP/PFS/EFS</th>
<th>Overall Survival (months)</th>
<th>3 year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facon (Lancet 2007)</td>
<td>MPT</td>
<td>52</td>
<td></td>
<td>~65%</td>
</tr>
<tr>
<td>San Miguel (JCO 2010)</td>
<td>VMP</td>
<td>NR*</td>
<td></td>
<td>69%</td>
</tr>
<tr>
<td>Rajkumar (Lancet Oncol 2010)</td>
<td>Rd</td>
<td>25</td>
<td>NR*</td>
<td>75% (Rd age ≥65)</td>
</tr>
</tbody>
</table>
Transplant Ineligible

- **High Risk**
  - VRd
  - Bortezomib-based maintenance

- **Intermediate Risk**
  - VCd
  - ~24 months

- **Standard Risk***
  - VCd or Rd
  - 12-18 months Rd- Can Continue till PD

v9 Revised and updated: Jun 2011
MP-plus Regimens: MPR

Overall Survival

Patients (%) vs. Time (months)

- MPR-R
- MPR
- MP

TD versus MP

B Progression-free Survival by Therapy

- MP: n = 141, 72 events, median = 20.7 months
- Thal-Dex: n = 142, 84 events, median = 16.7 months

HR 1.3 (95% CI: 0.95-1.78) $P = .10$, logrank test, two-sided

No. At Risk
n = 141 83 48 26 14 7 4  (MP)
n = 142 77 43 27 16 7 1  (Thal-Dex)

Follow-up (months)

C Overall Survival by Therapy

- MP: n = 141, 47 events, median = 49.4 months
- Thal-Dex: n = 142, 64 events, median = 41.5 months

HR 1.55 (95% CI: 1.06-2.27) $P = .024$, logrank test, two-sided

No. At Risk
n = 141 103 71 42 25 13 5  (MP)
n = 142 87 63 36 22 10 3  (Thal-Dex)

Follow-up (months)
RISK-ADAPTED THERAPY

- **BIOLOGY**
  - High Risk: VRd
  - Intermediate Risk: VCd
  - Standard Risk: Rd or VCd

- **STAGE**
  - PCL, EMD: VDT-PACE
  - ARF: VCD or VTD

- **HOST**

  - *Once weekly Dex (except VDT-PACE)*
  - *Once weekly bortezomib (except ARF; VDT-PACE)*

HAEMATOLOGICAL CANCER

Redefining myeloma

S. Vincent Rajkumar, Giampaolo Merlini and Jesus F. San Miguel

The current definition of multiple myeloma is outdated. The diagnosis requires evidence of overt end-organ damage, preventing initiation of early therapy when the malignancy is at its most susceptible stage. We propose an evidence-based approach using more-sensitive and highly specific biomarkers to update the definition of this disease.


Multiple myeloma is unique among cancers in that a clinician’s opinion on whether or not ‘end-organ’ damage is present is required to make a diagnosis of malignancy. The distinction between MGUS and myeloma, in which the risk of progression to malignancy in the first 5 years following diagnosis is 10% per year,5 SMM includes a heterogeneous population that treatment options for myeloma, until recently, were limited; alkylators, cortico-

Myeloma Treatment

Aggressive therapy

- Triplet or quadruplet induction
- Early transplant
- Lenalidomide maintenance

“Cure” Approach

Sequential Therapy

- Doublet or “mild” triplet induction
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“Control” Approach