Upfront Therapy for Myeloma
Tailoring Therapy across the Disease Spectrum
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Mayo Clinic

Scottsdale, Arizona
Rochester, Minnesota
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# 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 $\geq 2.0$)</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>

HOST FACTORS

- Age, performance status, comorbidities
- Renal Failure
TUMOR BURDEN (STAGE)
# Tumor Biology: Disease Aggressiveness

## Myeloma Risk-Stratification

<table>
<thead>
<tr>
<th>High-Risk</th>
<th>Intermediate-Risk</th>
<th>Standard-Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del 17p</td>
<td>t(4;14) (FGFR3/MMSET)</td>
<td>All others including:</td>
</tr>
<tr>
<td>t(14;16) (C-MAF)</td>
<td></td>
<td>- Hyperdiploid</td>
</tr>
<tr>
<td>t(14;20) (MAF-B)</td>
<td></td>
<td>- t(11;14) (CCND1)</td>
</tr>
<tr>
<td>GEP</td>
<td></td>
<td>- t(6;14) (CCND3)</td>
</tr>
</tbody>
</table>

*Presence of trisomies ameliorates high 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)

CR appears critical

Bortezomib Critical

Excellent Outcome

*Presence of trisomies ameliorates high risk
CR is critical in patients with high-risk myeloma

Low-Risk MM (87%)

High-Risk MM (13%)

Principles

• Randomized trials
• Evidence of clinical benefit
  • Survival or
  • QOL
• Estimated prognosis (Risk-Adapted Therapy)
• Toxicity and Convenience
• Cost
Principles

Risk-adapted ≠ “Weak therapy for good risk patients”

• Avoid unproven therapies in good-risk patients
  • Toxicity
  • QOL
  • Cost

• Patient wishes and tolerance to risk
Approach

**Transplant Eligible**

- Melphalan-Containing Regimens
- Non Melphalan Containing Regimens

**Transplant Ineligible**

- Melphalan-Containing Regimens
- Non Melphalan Containing Regimens
Approach

**Transplant Eligible**
- Melphalan-Containing Regimens
- Non Melphalan Containing Regimens

**Transplant Ineligible**
- Melphalan-Containing Regimens
- Non Melphalan Containing Regimens
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
Can 3 or more drug regimens provide additional benefit?

<table>
<thead>
<tr>
<th>Doublets</th>
<th>Triplets</th>
</tr>
</thead>
<tbody>
<tr>
<td>• TD</td>
<td>• VTD</td>
</tr>
<tr>
<td>• RD</td>
<td>• VRD</td>
</tr>
<tr>
<td>• VD</td>
<td>• VCD</td>
</tr>
</tbody>
</table>
VTD versus VD
Progression-free survival.

VTD vs TD
Progression free survival

Cavo et al. Lancet 2010
VTD vs TD: OVERALL SURVIVAL

HR, 0.76 [CI: 0.46-1.27]  
\( p = 0.3071 \)

Probability at 3 yrs (%)  
\[ \begin{array}{c|c|c} & VTD & TD \\ \hline 3 \text{ yrs} & 87 & 84 \\ \hline \end{array} \]  
\( p = 0.3042 \)
VRD

Efficacy: Overall

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

\[
67%* = \left\{ \begin{align*}
CR & : 29% \\
nCR & : 11% \\
VGPR & : 27%
\end{align*} \right. \\
\text{PR (33%)}
\]

- Overall response rate: 100%

Richardson PG. Blood 2010;116:679-686
Rd versus VRd

SWOG/ECOG S0777: Phase III – New MM

Randomization:
- Rd
- VRd

Branching:
- CR/PR/Stable → Continue therapy till prog. or toxicity
- Prog. anytime → Off Rx
<table>
<thead>
<tr>
<th>Response, %</th>
<th>VCD (n = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/nCR</td>
<td>41%</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>60%</td>
</tr>
<tr>
<td>ORR (≥ PR)</td>
<td>90%</td>
</tr>
</tbody>
</table>

Reeder C. Blood 2010
## 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>( \geq ) VGPR</td>
<td>58%</td>
<td>51%</td>
<td>44%</td>
</tr>
<tr>
<td>ORR (( \geq ) PR)</td>
<td>88%</td>
<td>85%</td>
<td>82%</td>
</tr>
</tbody>
</table>

Can 3 or more drug regimens provide additional benefit?

**Doublets**
- TD
- RD
- VD

**Triplets**
- VCD
- VTD
- VRD
Can 3 or more drug regimens provide additional benefit?

**Doublets**
- RD
- VD

**Triplets**
- VCD
- VTD
- VRD
Can 3 or more drug regimens provide additional benefit?

Doublets
• RD

Triplets
• VCD
• VTD
• VRD
Can 3 or more drug regimens provide additional benefit?

Doublets
- RD

Triplets
- VCD
- VRD
ECOG E4A03 Trial: Implications for Dex Dosing

Survival probability

Remaining at risk

Number at risk

Dex Dosing in Newly Diagnose Myeloma

**Doublets**
- Td
- Rd
- Vd

**Triplets**
- VCd
- VTd
- VRd
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)

CR appears critical
Bortezomib Critical
Excellent Outcome

*Presence of trisomies ameliorates high risk
Transplant Eligible

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

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

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


v9 Revised and updated: Jun 2011
TRANSPLANT INELIGIBLE
Initial Therapy: Non-Transplant Candidates

Estimated percentage still alive

- □ - allocated cct (% ± SD)
- ○ - allocated MP (% ± SD)

MTCG. J Clin Oncol 1998; 16:3832
MP-plus Regimens

### MPT
- **Treatment**
  - MP: 128/196
  - MPT: 62/125
  - MEL100: 78/126
- **Overall survival time (months)**
  - MP: 33.2 (3.2)
  - MPT: 51.6 (4.5)
  - MEL100: 38.3 (2.7)

### VMP

- **Surviving Patients (%)**
- **P = 0.008**

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Facon T. Lancet 2007;370:1209
MP-plus Regimens: MPR

Overall Survival

## Options in Transplant Ineligible Patients

<table>
<thead>
<tr>
<th>Non-melphalan based</th>
<th>Melphalan based</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Rd</td>
<td>• MPT</td>
</tr>
<tr>
<td>• VCd</td>
<td>• VMP</td>
</tr>
<tr>
<td>• VRd</td>
<td></td>
</tr>
</tbody>
</table>
## Options in Transplant Ineligible Patients

<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>28</td>
<td>52</td>
<td>~65%</td>
</tr>
<tr>
<td>San Miguel (JCO 2010)</td>
<td>VMP</td>
<td>24</td>
<td>NR*</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>

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

### Melphalan based
- MPT
- VMP
Options in Transplant Ineligible Patients

Non-melphalan based
- Rd
- VCd
- VRd

Melphalan based
- MPT
- VMP

FIRST TRIAL

MPT vs Rd
Options in Transplant Ineligible Patients

Non-melphalan based:
- Rd
- VCd
- VRd

Melphalan based:
- MPT
- VMP

FIRST TRIAL
MPT vs Rd
Options in Transplant Ineligible Patients

Non-melphalan based
- Rd
- VCD
- VRd

Melphalan based
- **MPT**
- **VMP**

FIRST TRIAL
MPT vs Rd
Options in Transplant Ineligible Patients

Non-melphalan based

- Rd
- VCd
- VRd
Transplant Ineligible

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

- **Intermediate Risk**
  - VCD
  - ~24 months

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

v9 Revised and updated: Jun 2011
TD versus MP

B  Progression-free Survival by Therapy

![Graph showing progression-free survival by therapy with details: 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.]

C  Overall Survival by Therapy

![Graph showing overall survival by therapy with details: 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.]

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VMP vs VTP Trial: Implications for Bortezomib Dosing

Lower risk of grade 3 or higher neuropathy with once-weekly dosing of VMP 13% (twice-weekly-VISTA) vs 7% (once-weekly)

Mateos M. Lancet Oncol 2010; 11: 934–941
VMP vs VMPT Trial: Implications for Bortezomib Dosing

Lower risk of grade 3 or higher neuropathy with once-weekly dosing of VMP or VMPT
16% (twice-weekly; n=134) vs 3% (once-weekly; n=369)
Newly Diagnosed Myeloma with special circumstances

- Plasma cell leukemia (PCL)
- Extensive extramedullary disease (EMD)
- Acute renal failure due to cast nephropathy
Plasma cell leukemia or multiple extramedullary plasmacytomas

VDT-PACE x 2 cycles ASCT, if eligible

Bortezomib maintenance

Usmani S. Leukemia 2012
Acute renal failure: Cast Nephropathy

Biopsy proven, or Presumptive (ARF with FLC ≥ 150 mg/dL

- VCD or VTD
- Plasma exchange and
- If needed hemodialysis

Newly Diagnosed Myeloma

High Risk
- VRD

Intermediate Risk
- VCD

Standard Risk
- Rd or VCD

PCL, EMD
- VDT-PACE

ARF
- VCD or VTD

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