MYELOMA MAINTENANCE
BEST PRACTICES:
POST THERAPY & POST
TRANSPLANT
INTRODUCTION
Clonal plasma cell malignancy leading to CRAB (hyperCalcemia, Renal failure, Anemia, Bone lesions) but also immune dysfunction, osteopenia, amyloidosis, etc...

Estimated 24,050 new cases in 2014 and >83,000 individuals living with the disease
At least seven new drugs approved in the last ten years

Most important and revolutionary are the so-called “novel agents”

- Proteosome Inhibitors: Bortezomib, Carfilzomib
- IMiDS: Thalidomide, Lenalidomide, Pomalidomide

Have led (generally) to a move away from cytotoxic chemotherapy
NEW AGENTS HAVE PRODUCED SURVIVAL GAINS

5-year survival:
29.8% → 32.7 → 35.2% → 39.6%

Median survival
3.2 vs 5 years

Sant et al. 2014.
Kumar et al. 2014.
BENEFITS HAVE NOT EXTENDED EQUALLY TO ALL PATIENTS

Table 3. Risk stratification and possible therapeutic questions within each risk categories

<table>
<thead>
<tr>
<th>Parameters</th>
<th>High-risk</th>
<th>Standard-risk</th>
<th>Low-risk</th>
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<tbody>
<tr>
<td>ISS II/III and (t(4;14) or 17p13 del</td>
<td>2 years 20%</td>
<td>Others</td>
<td>ISS I/II and absence of t(4;14), 17p13 del and +1q21 and age &lt;55 years</td>
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<tr>
<td>Median OS % Patients</td>
<td>2 years 20%</td>
<td>7 years 60%</td>
<td>&gt;10 years 20%</td>
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Avet-Louise. 2013.
Chng. 2014.
RELAPSE REMAINS A PROBLEM

Sahebi et al. BJH. 2013.
Prolonged therapy given after initial therapy to prolong or deepen response

- Maintenance: >1 year
- Consolidation: ≤1 year
JUSTIFICATIONS TO FOCUS ON CONSOLIDATION / MAINTENANCE

- Incremental benefit with additions to upfront therapy?

- Therapy better tolerated in a minimal disease state?

- Increased chemo-sensitivity in minimal disease state?

- Increased survival? Cure?
CONFUSION: DOES ABILITY TO GIVE MORE THERAPY HELP SURVIVAL?

Response after primary therapy

- Autologous stem cell transplant (category 1) →
  - Response or stable disease →
    - Maintenance therapy
    - Second tandem transplant
    - Observe
  - or
    - Allogeneic stem cell transplant in clinical trial
  - or
    - Continue myeloma therapy until best response →
      Monitor as above and/or maintenance therapy

THERE IS A TENDENCY FOR DOGMATISM

- Debates about “maintenance yes” or “maintenance no” are published and discussed at meetings.

- These binary arguments don’t reflect actual medical decision making, and often argue past each other invoking different benefits.

- This is confusing and somewhat frustrating to everyone...
"Don't over-treat incurable disease"  
"Don't miss a chance to prolong life / prevent complications"

There is not currently evidence to support a single universal approach to maintenance therapy.

"You’re making more resistant disease"  
We might cure people
What maintenance and consolidation strategies have been studied?

What are the benefits of maintenance/consolidation therapy in terms of progression free and overall survival?

What are the risks of maintenance and consolidation therapies?

Which patients are most likely to benefit from maintenance or consolidation therapy?

How can we help our patients apply their interests/values to the decision of whether to use maintenance/consolidation therapy?
OUTLINE

- History of maintenance in MM / Learning from our mistakes
- Current maintenance / consolidation strategies and their impact
- Risks / costs of consolidation and maintenance therapy
- Who is likely to benefit
- Possible paths forward
- Questions
HISTORY OF MAINTENANCE IN MM
**CHEMOTHERAPY**
- Attempted to use alkylators in a prolonged fashion (mostly melphalan)
- Led to unreliable PFS improvement, no suggestion of OS improvement; creates high risk of 2\textsuperscript{nd} cancers

**INTERFERON**
- Huge metaanalysis suggests small PFS and very small OS improvement (2\% \pm 1.7\% at 5 years)
- Inconvenient and difficult to deliver so stopped

Conclusion: May have small benefit that subsequent AE risk overwhelms in general, probably not best current option
Conclusion: Almost certainly a benefit in those with bone disease, probably a useful adjuvant.
Conclusion: Likely some people benefitted but difficult to tolerate and unlikely to regain popularity in the US**
SUMMARY

- Alkylator chemotherapy is NOT effective as maintenance

- IFN maintenance inconvenient, expensive, and has marginal effect so largely discarded

- Steroid maintenance may have small benefit but dose difficult and risk/benefit precarious, not generally recommended

- IV bisphosphonate may have OS benefit, and have a good reason to use

- Thalidomide has a reproducible PFS benefit, prolonged follow up has showed an inconsistent OS benefit & agent supplanted in the US by lenalidomide
MAINTENANCE/CONSOLIDATION STRATEGIES: TRANSPLANT INELIGIBLE
**BORTEZOMIB-THALIDOMIDE (VT) MAINTENANCE**

- Large Italian study of transplant ineligible patients

- VMPT (bort/melphalan/thal/pred) → VT (2 years) vs VMP → observation

- PFS and OS better in the quadruplet and maintenance arm

- Unclear if this is an induction or maintenance effect

- Unlikely to become a common US induction regimen

Len maintenance after MPR induction, MPR alone, or MP
- Maintenance prolongs PFS (by 17 mos)
- No OS improvement with len maintenance or any induction regimen

Lenalidomide/dexamethasone (Rd) indefinitely vs 18 mos vs MPT for 18 mos

- PFS improved 7 mos w/ maintenance
- OS of continuous arm > MPT arm (59 vs 51% at 4 years)

Palumbo et al. NEJM. 2012; Benboubker. NEJM. 2014.
VMPT → VT maintenance seems to improve PFS and OS over VMP without maintenance, the maintenance component of therapy was well tolerated.

Lenalidomide maintenance after MPR prolongs PFS without OS benefit.

Continuous Rd provides excellent PFS and OS in older patients with MM with less toxicity than a triplet regimen, limited course showed worse PFS but OS not significantly worse.
MAINTENANCE AND CONSOLIDATION: TRANSPLANT ELIGIBLE
Lenalidomide after autoSCT leads to about an 18 month increase in PFS.
LENALIDOMIDE AFTER AUTOSCT: OVERALL SURVIVAL

IFM2005-2

Calculated for survival data:

- **Overall Survival (%)**
- **Months of Follow-up**

**NO OS Benefit!**

P = 0.29

CALGB100-104

Calculated for survival data:

- **Probability of Overall Survival**
- **Months since Autologous HSCT**

**Statistically significant OS benefit**

15% vs 23% dead

P = 0.03

More mature data has borne out these initial findings, still PFS benefit and no OS in IFM; still OS benefit in CALGB

Attal. NEJM. 2012

McCarthy. NEJM. 2012.
LENALIDOMIDE MAINTENANCE AFTER AUTOSCT → AGAIN

- Len/Dex (Rd) → autoSCT or MPR → lenalidomide maintenance or observation

No OS benefit
HR 0.64, P=NS

This needs to mature
Rd still not optimal induction for this question

17.3 mos PFS benefit in transplant arm
One randomized trial from Europe (HOVON-65 / GMMG-HD4)

- Bortezomib, Doxorubicin, Dex (PAD) \(\rightarrow\) bortezomib maintenance
- Vincristine, Doxorubicin, Dex (VAD) \(\rightarrow\) thalidomide maintenance

PFS and overall survival advantage in the bortezomib containing arm, unclear if this due to induction or maintenance

This benefit was more marked in high risk patients

Sonneveld. JCO. 2012.
CONTINUOUS THERAPY WITH NOVEL DRUG TRIPLETS IN TRANSPLANT ELIGIBLE

**RVD**

Excellent PFS, good tolerability in patients selected

Overall survival data not clear yet

No good randomized data for this vs transplant based approaches (active area)

I do not tend to favor off trial, though there are patient situations where this may be reasonable


Randomized trial in Germany & Netherlands of bortezomib consolidation vs not after transplant:
- no bortezomib pre-transplant)
- 7 months PFS improvement (27 vs 20) with bortezomib after transplant FOR ONLY SIX MONTHS of therapy

French Phase II study:
- Bortezomib, Lenalidomide, & Dexamethasone (VRD) X3 then autoSCT then VRD X2 (then lenalidomide maintenance)

- Increase in at least VGPR rate and MRD negative rate at each step:
  - VGPR or better: 58% → 70% → 87%
  - MRD negative: 16% → 54% → 58%

CONSOLIDATION - LIMITED COURSE CAN DEEPEN RESPONSES

Roussel. JCO. 2014.
Lenalidomide maintenance yields ≈ 13-18 month PFS after autologous stem cell transplant

1/3 studies has shown an OS benefit from lenalidomide maintenance after autoSCT

Bortezomib maintenance probably prolongs PFS and OS but we lack a phase III trial to address this question specifically

Consolidation strategies may deepen initial responses and prolong PFS with more limited therapy, there is a lack of “clean” randomized data attesting to their benefit
COSTS OF CONTINUOUS THERAPY
Metanalysis of interferon and some thalidomide maintenance trials showed shorter survival after progression leading to same OS despite improved PFS.

May be an artifact of time of trials and lack of new agents when these trials were done.

Appears less of an issue in more recent trials.

PFS2 (time to second progression, third line therapy, or death) is being looked at as a marker for this.
A significant problem that may have limited efficacy of thalidomide and interferon maintenance

Newer regimens have been more manageable, due to reduced doses of induction regimen

THESE STUDIES ALL ARE PROBABLY BIASED TOWARD PATIENTS WHO TOLERATE THERAPY WELL

It is likely you are not helping the patient if they have more than mild toxicities (If it is affecting their day to day function it is probably too much)

PERSISTENT FUNCTIONALLY LIMITING TOXICITY MAY BURN A BRIDGE TO A NEW TRIAL OR AGENT
• In general risks of myeloma far overwhelm risks of a second cancer...
• Risks are highest when given with oral melphalan
• This risk is more concerning in a patient who has a very low risk of early death from myeloma
FINANCIAL COSTS

Daily lenalidomide after autologous stem cell transplant: $205,500/yr

Based on 3 year OS NNT 12.5 = $5,000,000+ to prevent a death

Bortezomib per HOVONN schema after autologous stem cell transplant = $37,000/yr

Compare to autologous stem cell transplant = $91,000 → 60,000 if outpatient

Based on 4 year OS NNT 6.1 = $555,100 to prevent a death

Majhail et al. 2013.
Holbro et al. 2013.
IDENTIFYING PATIENTS WHO ARE LIKELY TO BENEFIT
HOW DEEP A RESPONSE DO WE NEED?

SYMPTOMATIC MYELOMA

VGPR

CR

STRINGENT CR
MRD NEGATIVE CR

“CURE”
VGPR = immunofixation detectable M-spike but not detectable by standard SPEP

French combined analysis of early transplant trials showed that EFS (42 vs 32 months) and 5 year OS (74% vs 61%) were significantly better in patients achieving at least a VGPR (Harousseau. JCO. 2009.)
- This benefit was more pronounced in patients with higher risk disease

French data suggesting second autologous transplant (“Tandem transplant”) only benefitted those who did not achieve at least VGPR with first (Attal. NEJM. 2003.)

THESE ARE TRANSPLANT TRIALS, harder to set a level for non-transplant
6 months of Proteosome inhibitor consolidation converted some patients to ≥ VGPR level of response

58/182 patients converted from sub-VGPR response to ≥ VGPR

These patients did as well as those who obtained VGPR earlier in therapy with PFS 12 months longer than those who didn’t

NNT = 4.5 patients to convert one patient to ≥ VGPR

Price for total treatment: $102,816

Price for one year of proteosome and lenalidomide based triplet = $200,000

CAN WE HELP PATIENTS WITH HARDER TO TREAT DISEASE?

Table 1. Standard Risk Factors for MM and the R-ISS

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Criteria</th>
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<tr>
<td>ISS stage</td>
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<tr>
<td>I</td>
<td>Serum β₂-microglobulin &lt; 3.5 mg/L, serum albumin ≥ 3.5 g/dL</td>
</tr>
<tr>
<td>II</td>
<td>Not ISS stage I or III</td>
</tr>
<tr>
<td>III</td>
<td>Serum β₂-microglobulin ≥ 5.5 mg/L</td>
</tr>
<tr>
<td>CA by iFISH</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)</td>
</tr>
<tr>
<td>Standard risk</td>
<td>No high-risk CA</td>
</tr>
<tr>
<td>LDH</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>Serum LDH &lt; the upper limit of normal</td>
</tr>
<tr>
<td>High</td>
<td>Serum LDH &gt; the upper limit of normal</td>
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A new model for risk stratification for MM

R-ISS stage

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<tbody>
<tr>
<td>I</td>
<td>ISS stage I and standard-risk CA by iFISH and normal LDH</td>
</tr>
<tr>
<td>II</td>
<td>Not R-ISS stage I or III</td>
</tr>
<tr>
<td>III</td>
<td>ISS stage III and either high-risk CA by iFISH or high LDH</td>
</tr>
</tbody>
</table>

Overall Survival (probability)

Median OS

- R-ISS I: NR
- R-ISS II: 83 months
- R-ISS III: 43 months

Time (months)

0 12 24 36 48 60 72

Palumbo. JCO. 2015.
From PAD vs VAD trial

Bortezomib (arm B) seemed to partially ameliorate poor outcomes with 17p- in PAD vs VAD trial.

HIGH RISK MYELOMA

Neben et al. 2012.
Bergsagel et al. 2013.

No trial has been able to overcome increased risk of high risk disease.
LENALIDOMIDE MAINTENANCE FOR HIGH RISK MYELOMA?

No compelling evidence that lenalidomide maintenance significantly ameliorates high risk
Phase II trial from Emory

- 45 very high risk patients
- 42% 17p deletion, 34% PCL, others 4:14, 14:16, or 1q abnormalities
- RVD $\rightarrow$ AutoSCT $\rightarrow$ Started on RVD after transplant (weekly bortezomib, weekly dexamethasone, and 1-21 lenalidomide) up to three years then single agent lenalidomide

- 96% > VGPR
- PFS = 32 mos

- Usual OS in this population would be around 2 years

Patients without at least VGPR likely to benefit from consolidation / maintenance approaches to get deeper response.

Bortezomib based maintenance appears to help diminish the increased risk associated with high risk multiple myeloma.

Lenalidomide maintenance alone DOES NOT show compelling evidence of attenuating increased hazard of high risk disease.

For fit patients with very high risk myeloma with abnormalities of p53 (17p), t(14:16), t(14:20), or PCL clinical trials remain the best option.

- RVD induction and consolidation after transplant seem offer improved survival for patients who cannot be treated on trial.
THE WAY FORWARD
- BMT CTN 0702
  - RVD → autoSCT → 2\(^{nd}\) autoSCT → R maintenance
    → RVD consolidation → R maintenance
    → R maintenance

- IFM/DFCI 2009 – RVD with or without transplant up-front

- E1A11: 2 years maintenance vs indefinite maintenance

- EMN trial: VRD consolidation or not after transplant
Checkpoint inhibitors: being studied in relapsed/refractory disease with IMiD and alone after transplant

Incorporation of antibody therapies into upfront therapy likely to move to maintenance approaches (see low grade lymphoma)

Mayo Clinic Virus Therapy

Dendritic cell/macrophage targeted vaccine and other trials

CAR – T cell therapy (very early data <10 pts in relapsed disease)
More widely applicable minimal residual disease testing and response adapted trials (i.e. randomize patients to consolidation/maintenance strategies depending on their response to upfront therapy)

Further study of risks / benefits of continued therapy for relapsed / refractory disease

RESEARCH AND TRIALS REMAIN CRITICALLY IMPORTANT EVEN AS OUTCOMES IMPROVE
Transplant Ineligible:
- Continuous Rd provides a PFS benefit over the same regimen for 18 months
- No data clearly favoring an optimal approach for high risk patients, reasonable to extrapolate transplant eligible data and aim for bortezomib based maintenance though toxicity may be more problematic

Transplant eligible
- Patients who do not achieve at least VGPR post transplant may benefit from further consolidation, we typically favor an additional 2-4 cycles of their initial regimen
- Continuous treatment with frontline novel agent based triplet is promising and being studied further
Transplant Eligible Maintenance By Risk Group

- Low or standard risk myeloma without high risk cytogenetics
  - PFS benefit for lenalidomide post transplant (≈18 mos)
  - No consistent data suggesting an overall survival benefit (indefinite maintenance usually favored over 2 years, for now)

- High risk patients
  - Bortezomib maintenance likely prolongs overall survival, 2 years is usually duration of PI based maintenance

- Very High risk patients (17p-, t(14:16), t(14:20) or PCL)**
  - Clinical Trial best
  - Off trial RVD consolidation and indefinite maintenance may have additional benefit.

** Moving target**
ALL OF THESE APPROACHES HAVE SIDE EFFECTS, DANGERS, AND BENEFITS. WITHOUT COMPELLING EVIDENCE OF SURVIVAL BENEFIT IT IS CRUCIALLY IMPORTANT WE INVOLVE PATIENTS IN A VALUES-BASED DISCUSSION OF MAINTENANCE DECISIONS.
QUESTIONS?
THANK YOU