

Maintenance Therapy after Transplant: Multiple Myeloma

Celebrating a Second Chance at Life Survivorship Symposium

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Learning Objectives

1. Why maintenance therapy is needed
2. Which maintenance therapies are used and for how long
3. Length of disease control on maintenance therapies
4. Potential side effects of maintenance therapies
5. Additional therapies available when disease progresses on maintenance therapy

What We are talking About (and Not Talking About)

Our Topic

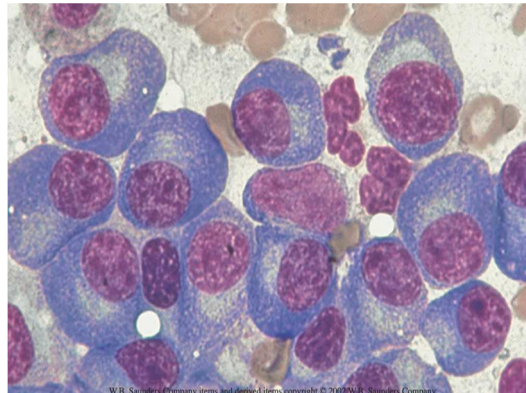
- Multiple myeloma
- Autologous stem cell transplant
- Transplant as part of treatment for newly diagnosed myeloma
- Maintenance therapy

Other Topics

- Lymphoma, leukemia, amyloidosis, smoldering myeloma
- Allogeneic (donor) stem cell transplant
- Transplant as treatment for relapsed or refractory myeloma
- Consolidation therapy

Myeloma Diagnosis

- Cancer of malignant plasma cells
- Diagnosed by finding
 - clonal plasma cells in the bone marrow
 - abnormal antibody proteins in the blood and urine



Myeloma Symptoms and Management

CRAB(i) criteria

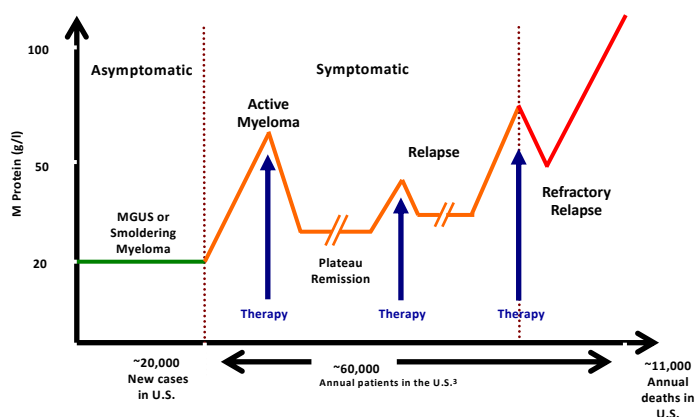
- High **c**alcium levels
- Kidney (**r**enal) injury
- **A**nemia (low red blood cells)
- **B**one destruction (“lytic bone lesions”)
- Risk of **i**nfection

Symptom management

- Medicines to lower calcium levels and reduce fracture risk
- Radiation and pain medication for bone pain
- Red blood cell growth factors for anemia
- Kidney Protection
- Vaccinations and antibiotics

Myeloma Disease Course

- Effective treatments but no cure
- Multiple courses of treatment, with response followed by eventual progression
- Over time, lower chance of response and shorter duration of response



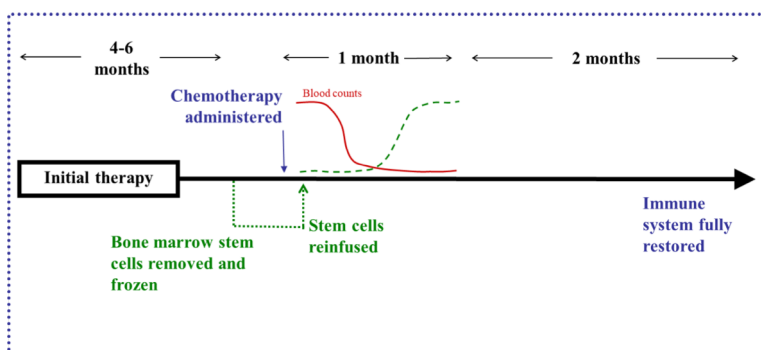
1. Adapted from International Myeloma Foundation; 2001. Reprinted with permission.
2. American Cancer Society. Cancer Facts & Figures; 2003. 3. Millennium Pharmaceuticals, Inc., 2003.

Available Treatments for Myeloma

- Steroids (dexamethasone, prednisone)
- IMiDs (lenalidomide, pomalidomide, thalidomide)
- Proteasome inhibitors (bortezomib, carfilzomib, ixazomib)
- Antibodies (daratumumab, isatuximab, elotuzumab)
- Cytotoxics (cyclophosphamide, melphalan, doxorubicin)
- Newer agents (selinexor, venetoclax)
- CAR T cells (ide-cel, cilta-cel)
- T cell engagers (teclistamab)

Autologous Transplant for Myeloma

- The treatment is high-dose chemotherapy
- Stem cells rescue blood counts that would otherwise take months to recover



What is Maintenance Therapy?

**Additional treatment given in the setting of a response
that contributes to longer disease control**

- After standard-dose therapies, can also be called “continued therapy”
- After high-dose chemotherapy and stem cell transplant, usually consists of additional treatment started several months later

Reasons to Use Maintenance Therapy for Myeloma

Possible reasons

- Deepen response and eliminate minimal residual disease
- Stimulate immune response
- Avoid development of resistance mutations
- Prolong disease response

The real reason (in my opinion)

- Improve overall survival

Maintenance Treatments with Proven Benefit in Myeloma

Lenalidomide (Revlimid)

- 4 randomized clinical trials comparing Len to placebo or no treatment
- Improved overall survival (even though Len was available at progression)
- Confirmed in a meta-analysis combining trial data

Bortezomib (Velcade)

- 1 randomized clinical trial of bortezomib pre-transplant and in maintenance, compared to thalidomide-based treatment
- Improved overall survival

Other Maintenance Treatments That Have Been Tried in Myeloma

Not commonly used

- steroids
- thalidomide (Thalomid)
- ixazomib (Ninlaro)

(these have had clinical trials showing limited or no benefit)

Used in some situations

- Lenalidomide combinations
 - + bortezomib
 - + carfilzomib
 - + daratumumab

- Pomalidomide (alone or in combination)

(these have limited data but possible benefit)

Typical Plan for Lenalidomide Maintenance

- Maintenance therapy starts 90-180 days after transplant
- Lenalidomide dosing:
 - Start at 10 mg daily
 - Consider dose increase to 15 mg daily after 3 months
- Schedule: dose on days 1-21 of 28 (3 weeks on / 1 week off) OR days 1-28 of 28 (continuous)
- Dose adjustments for side effects:
 - Decrease to 10 mg daily, 5 mg daily, or 5 mg every-other-day

Side Effects of Lenalidomide Maintenance

- Common side effects (usually mild)
 - Fatigue
 - Diarrhea
 - Rash (or itching)
 - Low blood counts (especially neutrophils)
 - Muscle cramps
- Risk of blood clots (daily aspirin needed)
- Less common: Neuropathy

Second Cancers with Lenalidomide Maintenance

- Three trials showed a higher risk of second primary malignancies with len maintenance after autologous stem cell transplant
- Biggest increase in risk was second hematologic (blood and bone marrow) cancers: leukemia and myelodysplastic syndrome (MDS)
- However, the risk of myeloma relapse was higher than the risk of second malignancies in both patients on len and on placebo
- No evidence that the risk of death from second cancers outweighs the benefit of len in prolonging overall survival

Duration of Lenalidomide Maintenance

- No good data on the optimal duration of maintenance
- Trials used indefinite maintenance (until progression)
- Concerns about second malignancies have led to some experts (especially in Europe) to recommend fixed-duration (1-2 years)
- For most patients in the U.S., we use indefinite maintenance:
 - Until progression
 - Or intolerable side effects
 - Or the patient really wants to stop

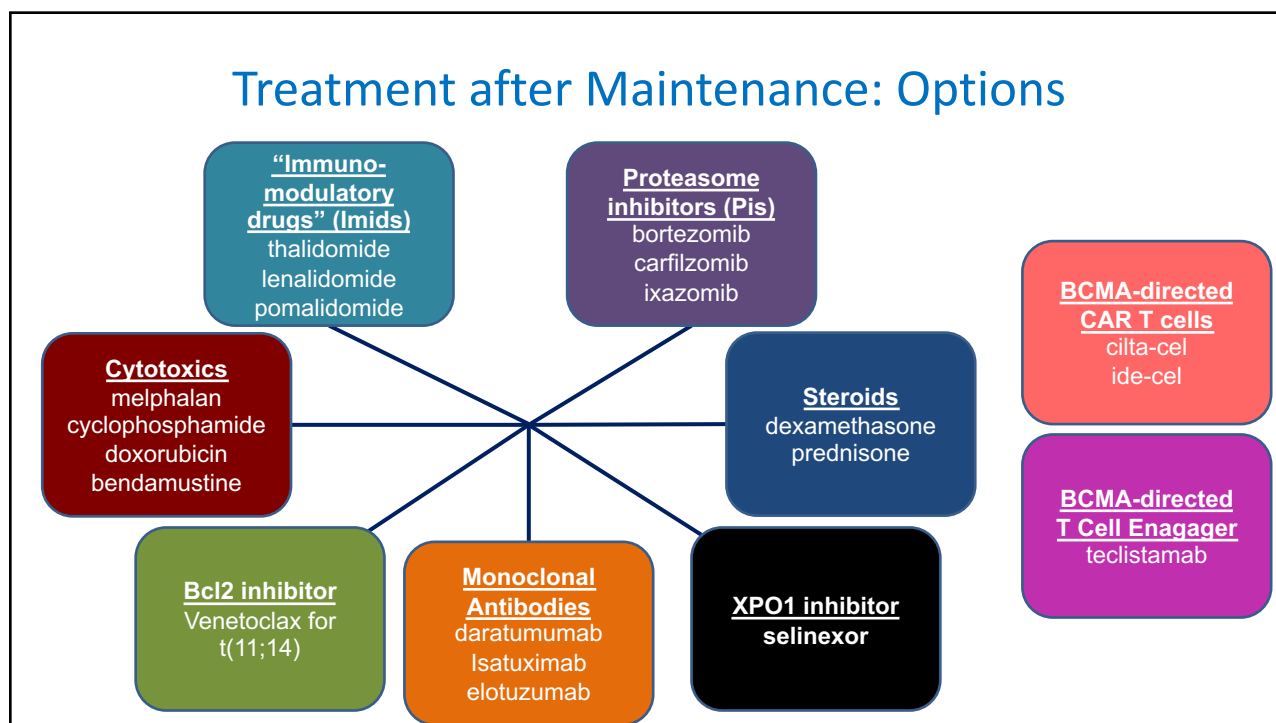
Duration of response with Lenalidomide Maintenance

- Average (median) duration of response ~4 years
- Wide range

Bortezomib Maintenance

- Maintenance therapy usually starts 90-180 days after transplant
- Bortezomib:
 - Subcutaneous (under-the-skin) injection
 - Every 2 weeks
- Duration of maintenance therapy: 1-2 years (but can be indefinite)
- Side effects: Fatigue, low blood counts (especially platelets), neuropathy, risk of shingles (acyclovir)

Treatment after Maintenance: Options



Treatment after Maintenance: Combinations

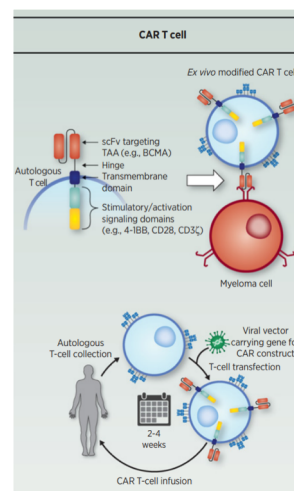
- Most patients should receive a triplet therapy
- The most common triplets are:
 - Daratumumab (or isatuximab) combinations: DRd, DVd, DKd, DPd
 - Imid/PI combinations: VRd, KRd, VPd, KPd, IRd, Ipd
 - Cyclophosphamide combinations: CyBorD, CyCarDex
- Later line therapies:
 - Elotuzumab combinations: elo/Rd, elo/Pd
 - Selinexor combinations: XVd, XKd, DXd, XRd, XPd
- Important option for t(11;14) myeloma: venetoclax combinations

Treatment after Maintenance: Second Transplant?

- Limited data
- Duration of response correlates with response to first transplant
 - But rarely longer
- Most appropriate for patients with long response to first transplant

Treatment after Maintenance: CAR T cells

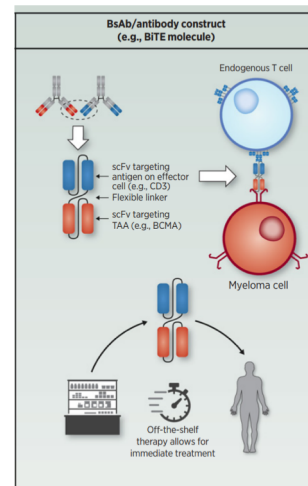
- Genetic retargeting of immune T cells
- Requires T cell collection (shorter than stem cell collection), chemotherapy (less intense than a stem cell transplant), and T cell reinfusion (risk of cytokine release syndrome and neurotoxicity)
- Two products: ide-cel (Abecma) and cilta-cel (Carvykti)
 - Both target B cell maturation antigen (BCMA)



Cohen AD, et al. *Clin Cancer Res.* 2020;26(7):1541-54.

Treatment after Maintenance: T cell Engager

- Bispecific (double-headed) antibody targeting myeloma cell and T cell
- Induces a T cells attack on the myeloma cell, similar to CAR T cells
- No cell collection, no chemotherapy
- Ongoing subcutaneous dosing every 1-2 weeks
- One product: teclistamab (Tecvayli)
 - Targets BCMA



Cohen AD, et al. *Clin Cancer Res.* 2020;26(7):1541-54.

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Conclusions

- Maintenance therapy after transplant for myeloma is based on clinical trials showing improved overall survival
- The most common and most proven maintenance therapy is single-agent lenalidomide
- Side effects during maintenance are typically mild but often lead to dose reductions and sometimes to discontinuation
- Many options are available for treatment of myeloma that has progressed after maintenance therapy



QUESTIONS?

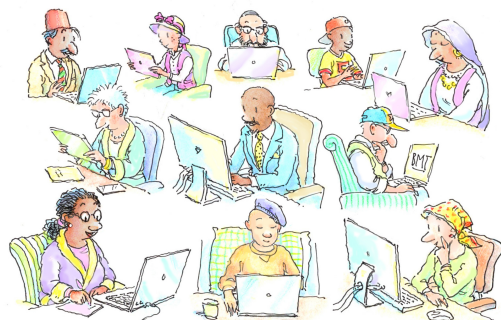


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