Atypical Presentation of Multiple Myeloma

Bassim Albeirouti, MD, MSC, CIP, FRCPC, FACP

Multiple Myeloma Site Leader

@ KFSHRC – Jeddah Branch
There is conflict of interest
I am on Advisory Board of Jansen Company
(The producer of Velcade® & Darzalex®)
The Royal College of Physicians and Surgeons of Canada

This is to attest that

Bassim Malas Al-Beirouti

has fulfilled the requirements for

Clinician Investigator Program

August 14, 2002

a special program accredited by the Royal College of Physicians and Surgeons of Canada

Le Collège royal des médecins et chirurgiens du Canada

Nous attestons par le présent que

Bassim Malas Al-Beirouti

a satisfait aux exigences du

Programme de formation de cliniciens-chercheurs

Le 14 août 2002

un programme spécial agréé par le Collège royal des médecins et chirurgiens du Canada

President / Président

Registrar / Directeur du registre
The Inside Story of a Patient With Multiple Myeloma, The Journey of Life

• The departure from normal life, my testimony.

• The journey of symptoms and signs & pain and gain history.

• The journey of investigations to reach the diagnosis.

• The journey of treatment as outpatient in OTA & OPD.

• The journey of ABMT & Admission to four north.

• The arrival to my final destiny peacefully and return back to my normal life.

• Thank you KFSHRC Jeddah Branch for restoring my life again and all the thanks to Allah before, during, and after everything in this memorable journey of life.
We are J & J. We are Married for years. We love each other for ever.
Standing together, Beside each other, as One Sole and two bodies
We are B & B. We are married for years. Behind every great man a greater woman, supporting and loving
We have our daughter, we are supporting our family, we will be always there, No matter where
The Inside Story of a Patient With Multiple Myeloma, The Journey of Life

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- Thank you KFSHRC Jeddah Branch for restoring my life again and all the thanks to Allah before, during, and after everything in this memorable journey of life.
I have severe backache, headache, bone ache, constipation, fatigue, tired, numbness of legs.
Forgive me my darling, I can not help you anymore in the garden, I fell down and broke my leg and I am on wheelchair now.
Content:

The Inside Story of a Patient With Multiple Myeloma, The Journey of Life

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What to request if you suspect any of Plasma Cell Dyscrasia (PCD) or MM

- You have to search for monoclonal protein or tissue plasma-cytomas and prove the target organ damage (TOD) as per the new criteria of diagnosis of PCD & MM
- TOD is defined as CRAB + N:
  1. Calcium high (Hypercalcemia)
  2. Renal Impairment & Proteinuria
  3. Anemia usually normocytic, normochromic
  4. Bone Lesions defined by skeletal surveys (only 30% sensitivity, more appropriately to use low dose CT with no contrast, or whole body MRI for soft tissues plasma-cytomas, or PET-CT is the best modality)
  5. & Neuropathies most commonly peripheral ones associated with IgM mainly
What to request if you suspect any of Plasma Cell Dyscrasia (PCD) or MM

- The search for monoclonal protein includes the following:
  1. SPEP (Serum Protein Electrophoresis & Immunofixation to determine the type if there is a monoclonal band)
  2. UPEP (Urine Protein Electrophoresis & Immunofixation to determine the type if there is a monoclonal band)
  3. SFLC (Serum Free Light Chain)
  4. UFLC (Urine Free Light Chain)
  5. Immunoglobulin Levels of IgG, IgA, IgM, and IgD if suspected
  6. Plasma-cytomas on tissue biopsy and monoclonal Plasma cells (BM)
  7. MYD 88 by molecular studies for WSM and LPL
  8. Kidney Biosy for LCD
  9. Bowel Biosy for HCD
  10. Congo Red Stain for Amyloidosis
Today I had too many x-ray and imaging. I wish we have a PET CT Scan here in Jeddah.
إيه يا بنتي ... لما صغيرة كنتي ...
خبيتك تحت جناحي ... خبيتك تترتاح ...
وكبيرة هلاً صرتي ... صرتي أنت جناحي ...
Content:
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• Thank you KFSHRC Jeddah Branch for restoring my life again and all the thanks to Allah before, during, and after everything in this memorable journey of life.
Why Velcade has to be given every Sunday ?!
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- Thank you KFSHRC Jeddah Branch for restoring my life again and all the thanks to Allah before, during, and after everything in this memorable journey of life.
The Journey of Admission for ABMT with the Transplant Team (R&H)
The Inside Story of a Patient With Multiple Myeloma, The Journey of Life

- The departure from normal life to a testimony.
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- **The arrival to my final destiny peacefully and return back to my normal life.**
- Thank you KFSHRC Jeddah Branch for restoring my life again and all the thanks to Allah before, during, and after everything in this memorable journey of life.
We hope that our BMT team got your satisfaction
The Inside Story of a Patient With Multiple Myeloma, The Journey of Life

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Thank you KFSHRC Jeddah Branch for restoring my life again and all the thanks to Allah before, during, and after everything in this memorable journey of life.
Thank you sir for having KFSHRC Jeddah Branch to look after your health & Do the ABMT for you. We hope that we met your expectations.
Multiple Myeloma; Treatment Options & Future Update

- Immune Therapy Era:
- Check Point Inhibitors Era
- CAR T cell Therapy Era
- Gamma/Delta T Cells Era
- **EMG, MM & PCL, WSM & LPL, LCD, HCD, ALA**
The Medical Paradigm in Multiple Myeloma

- Medicine is an Ever-Changing Science
- As New Research and Clinical Experience Broaden Our Knowledge,
- Changes in Treatment and Drug Therapy are Required.

*Williams Manual of Hematology 9th ed. 2017*
ASH Highlight of Multiple Myeloma; Transplantation, Consolidation, & Maintenance

- **Questions to be asked:**
- Transplantation
  - For which patients?
  - What is the age limit?
- Consolidation
  - What is the evidence?
  - Consolidation vs Tandem Transplant?
- Maintenance
  - For which patients or to all patients?
  - For how long or forever?
  - With which drug?
Questions Are Answered:

Transplantation:
- For all patients
- No age limit

Consolidation:
- There is a weak evidence
- Tandem Transplant is preferred

Maintenance:
- For all patients
- Forever
- Velcade Based vs Revlimid Based
ASH Highlight of Multiple Myeloma; Transplantation, Consolidation, & Maintenance

- **Answers to be Questioned:**
  - Transplantation:
    - Auto vs Allo vs Auto → Allo
    - Single vs Double (Tandem) vs Salvage
  - Consolidation:
    - Before BMT or after BMT
    - Double vs Triple vs Quadrable Drugs
  - Maintenance:
    - Value of Risk Stratification
    - Real Risks of Drugs
    - Velcade Based is probably better than Revlimid Based
Overall Trends in 2018

- MMRF CoMMpass™ Study to accelerate precision medicine
- Possible benefits of early treatment for high-risk smoldering MM (83% PR+)
- Role of induction, consolidation, and maintenance therapies before and after autologous stem cell transplant (ASCT) in newly diagnosed MM (NDMM)
- Darzalex™ (daratumumab) for early relapsed/refractory multiple myeloma (RRMM) and as upfront therapy in nontransplant and transplant eligible patients
- Novel therapies for highly pretreated RRMM
  - Keytruda® (pembrolizumab) PDL1- Check Point Inhibitor
  - Selinexor (CRM1 protein, exportin 1 or XPO1) a selective inhibitor of nuclear export
  - Chimeric antigen receptor T cells (CAR T cells), especially those directed against B-cell maturation antigen (BCMA)
Research Questions About NDMM

- Upfront ASCT is the standard of care in NDMM, but many patients relapse, even with complete response to ASCT.

- Can ASCT outcomes be improved with:
  - Double or “tandem” ASCT?
  - Triplet therapy using an immunomodulatory drug (IMiD) and a proteasome inhibitor (PI) for induction (before transplant)?
  - IMiD- and PI-based triplet therapy for consolidation (after transplant)?
  - Triplet therapy for BOTH induction and consolidation?

ASCT, autologous stem cell transplant; NDMM, newly diagnosed multiple myeloma.
Triplet Induction Therapy Before ASCT

- Phase 2 study update: induction therapy with KRd followed by ASCT and 2 years of REV maintenance (KRd-R)
- Excellent results:
  - Overall response rate (ORR) was 98%
  - Progression-free survival (PFS) at 48 months was 82%
  - Overall survival (OS) at 58 months was 86%
- Conclusion: KRd-R induction/maintenance produced deep complete responses (CR) regardless of age or genetic risks

ASCT, autologous stem cell transplant; KRd, Kyprolis (carfilzomib), Revlimid (lenalidomide), and dexamethasone; KRd-R, Kyprolis (carfilzomib), Revlimid (lenalidomide), and dexamethasone followed by Revlimid maintenance; REV, Revlimid (lenalidomide).

Single ASCT vs. Double ASCT vs. Single Plus Consolidation in NDMM

- StaMINA Phase 3 Trial – 3 study groups:
  - Single ASCT with REV maintenance
  - Double ASCT with REV maintenance
  - Single ASCT followed by consolidation with bortezomib (Velcade®; VEL), REV, and DEX (VRd) and then REV maintenance

- Results: PFS and OS were very similar in all 3 groups

- Conclusion: Addition of VRd consolidation or second ASCT was not superior to single ASCT followed by REV maintenance

ASCT; autologous stem cell transplant; NDMM, newly diagnosed multiple myeloma; OS overall survival; PFS, progression-free survival; REV, Revlimid (lenalidomide).
# Triplet Therapy Before and After Transplantation (IFM Studies)

<table>
<thead>
<tr>
<th></th>
<th>Moreau¹</th>
<th>Roussel²</th>
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</thead>
<tbody>
<tr>
<td>Triplet therapy for both induction and consolidation</td>
<td>IRd</td>
<td>KRd</td>
</tr>
<tr>
<td>Maintenance</td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Response rates (after consolidation)</td>
<td></td>
<td>R</td>
</tr>
<tr>
<td>VGPR or better</td>
<td>%80</td>
<td>%92.5</td>
</tr>
<tr>
<td>CR/sCR</td>
<td>%44</td>
<td>%69</td>
</tr>
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</table>

CR/sCR, complete response/stringent complete response; IRd, Ninlaro (ixazomib), Revlimid (lenalidomide), and dexamethasone; I, Ninlaro (ixazomib); KRd, Kyprolis (carfilzomib), Revlimid (lenalidomide), and dexamethasone; R, Revlimid (lenalidomide); VGPR, very good partial response.

**Conclusion:** IRd and KRd triplet therapy before and after transplant produced very good responses, but safety and efficacy remain open questions.

Relapsed/Refractory Multiple Myeloma

- **CASTOR** and **POLLUX** trials: Darzalex™ (Daratumumab) for RRMM

- 2016 approval based on CASTOR¹ and POLLUX² trials
  - twin multicenter, phase 3, randomized, open-label controlled trials of Darzalex™ (daratumumab; DARA) for patients with RRMM and a median of 2 prior lines of therapy

- Initial results were presented at ASCO and EHA meetings in June 2016
  - DARA resulted in >60% reduction in risk of disease progression or death in both studies

- New information: presentations at ASH 2016 examined different endpoints and broke down results within certain subgroups

ASCO, American Society of Clinical Oncology; EHA, European Hematology Association; RRMM, relapsed/refractory multiple myeloma.

Minimal Residual Disease and DARA

- **Minimal residual disease** (MRD) – more sensitive than traditional definitions of clinical response\(^1,2\)
- MRD-negativity is associated with longer PFS and OS in NDMM patients\(^1,2\)
  - MRD may become a primary endpoint for clinical studies
- Results: DARA induced MRD negativity in over 3 times as many patients as standard of care regimens

DARA, Darzalex (daratumumab); NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression-free survival.

DARA Outcomes by Subgroups

- Two additional studies\(^1,2\) grouped the CASTOR and POLLUX results into subgroups of patients based on several factors, including:
  - Number of prior lines of therapy (1 vs. 2–3)
  - High-risk cytogenetics
  - Refractoriness to prior lines
  - Treatment-free interval (time since last therapy)
- **Conclusion:** DARA was superior to the standard of care in all subgroups analyzed.

DARA, Darzalex (daratumumab).

**Venclexta® (Venetoclax) + Velcade (Bortezomib)**

- **Venclexta®** (Venetoclax; VEN) – formerly known as ABT-199
  - A BCL-2 inhibitor that is FDA approved for use in chronic lymphocytic leukemia
- **Rationale:** BCL-2 and MCL-1 both promote MM cell survival
  - VEL inhibits MCL-1, while VEN inhibits BCL-2
  - When used together, VEN enhances the efficacy of VEL
- **Goal:** MMRC phase 1b dose-escalation study of VEN + VEL + DEX in patients with RRMM to determine safety, efficacy, and optimal dose

DEX, dexamethasone; MM, multiple myeloma; RRMM, relapsed/refractory multiple myeloma; VEL (Velcade), bortezomib.

Venclexta Results

- ORR was 68%, and 40% achieved VGPR or better
- Response rates were higher in those with no prior VEL treatment, those not refractory to VEL, and those with fewer prior lines of therapy
- Responses were better in patients with a t(11;14) gene translocation than in those without the mutation
  - Can be used as targeted therapy for the t(11;14) high-risk subgroup

Conclusion: VEN + VEL + DEX has an acceptable safety profile and promising efficacy for RRMM, particularly in patients with a t(11;14) gene mutation

DEX, dexamethasone; ORR, objective response rate; RRMM, relapsed/refractory multiple myeloma; VEL, Velcade (bortezomib); VEN, Venclexta (venetoclax); VGPR, very good partial response.

Keytruda® (Pembrolizumab) + Pomalyst® (Pomalidomide) + DEX

- Patients (N = 9) had heavily pretreated RRMM
  - Median of 8 prior lines of therapy, including proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and ASCT
  - Previously exposed to Pomalyst (pomalidomide; POM)
- Acceptable safety profile, with adverse events similar to those seen in other studies of Keytruda (pembrolizumab) and POM
- ORR was 33%; clinical benefit rate (3 PR, 2 MR, 3 SD) was 89%

**Conclusion:** Results are promising; phase 3 studies of Keytruda (pembrolizumab) are now underway

ASCT, autologous stem cell transplant; CR, complete response; DEX, dexamethasone; MR, minimal response; PR, partial response; RRMM, relapsed/refractory multiple myeloma; SD, stable disease.

Selinexor and Proteasome Inhibitors

• In an MMRC phase 1 study,\(^1\) selinexor (SEL) was combined with Kyprolis™ (carfilzomib; CFZ) and DEX in patients with RRMM and at least 2 prior treatment regimens
• Even in patients who were CFZ-refractory, response rates were strong:
  – MR or better in 73%
  – PR or better in 64%
  – VGPR or better in 18%
• Similar results were seen in the phase 1b/2 STOMP\(^2\) trial, which used VEL as the PI instead of CFZ

Conclusion: Early clinical evidence suggests that SEL can overcome PI resistance in RRMM

DEX, dexamethasone; MR, minimal response; PI, proteasome inhibitor; PR, partial response; RRMM, relapsed/refractory multiple myeloma; SEL, selinexor; VEL, Velcade (bortezomib); VGPR; very good partial response.

Selinexor for Highly Refractory MM

• The STORM trial used SEL for patients highly refractory to previous combinations
  – All patients were at least “quad-refractory” to 2 IMiDs (both REV and POM) and 2 PIs (both VEL and CFZ)
  – Some patients were “penta-refractory” to both IMiDs, both PIs, plus 1 anti-CD38 antibody (DARA or isatuximab)
• ORR was 21% for quad patients and 20% for penta patients
• Clinical benefit rates (MR+) were 32% for all, 29% for quad, and 37% for penta

Conclusion: SEL shows promising anti-tumor activity in the quad- and penta-refractory MM populations, and expansion of this trial is planned

CFZ, Kyprolis (carfilzomib); DARA, Darzalex (daratumumab); IMiD, immunomodulatory drug; MR+, minimal response or better; ORR, overall response rate; PI, proteasome inhibitor; POM, Pomalyst (pomalidomide); REV, Revlimid (lenalidomide); SEL, selinexor; VEL, Velcade (bortezomib).
Anti-BCMA CAR T Cells

- Chimeric antigen receptor T cells (CAR T cells) – patient’s own
  - T cells are genetically modified to express chimeric antigen receptors (CARs) directed at MM antigens
  - After being genetically altered, cells are infused back into the patient
- BCMA is a promising target for CAR T-cell activity
- Current study evaluated anti-BCMA CAR T-cell infusion for treatment of advanced MM in heavily pretreated patients

BCMA, B-cell maturation antigen; MM, multiple myeloma.
Design and Results

- Ongoing phase 1 trial studying anti-BCMA CAR T cells alone or with cyclophosphamide
  - Patients had advanced RRMM, were IMiD and PI refractory, and had a median of 9 prior lines of therapy
- BCMA levels declined and correlated with depth of response
- Some severe toxicities were seen
- One patient showed anti-BCMA CAR T-cell persistence, with ongoing stringent complete response at 7 months and MRD-negative bone marrow

Conclusion: Anti-BCMA CAR T cells show promising expansion and clinical activity

BCMA, B-cell maturation antigen, CAR T cells, chimeric antigen receptor T cells; IMiD, immunomodulatory drug; MM, multiple myeloma; MRD, minimal residual disease; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma.

Other Promising Studies on BCMA and CAR T Cells

• A study in the preclinical evaluation stage is working on creating a treatment based on allogeneic (donor) anti-BCMA CAR T cells\(^1\)
  – CAR T cells that do not need to be custom made from each patient’s own cells could lead to an “off-the-shelf” immunotherapy for MM

• Other researchers showed that REV strengthens the anti-tumor activity of anti-CS1 CAR T cells in mice\(^2\)
  – Human trial planned using REV to enhance CAR T-cell activity

BCMA, B-cell maturation antigen, CAR T cells, chimeric antigen receptor T cells; MM, multiple myeloma; REV, Revlimid (lenalidomide); RRMM, relapsed/refractory multiple myeloma.
# Novel Therapies to Watch For

<table>
<thead>
<tr>
<th>Antibody (Target)</th>
<th>Proteasome inhibitors</th>
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<tbody>
<tr>
<td>B-B4, DL101 (CD(138)</td>
<td>Marizomib*</td>
</tr>
<tr>
<td>Indatuximab (CD(38)</td>
<td>Oprozomib</td>
</tr>
<tr>
<td>Lucatumumab (CD(40)</td>
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<tr>
<td>IPH-2101 (KIR)</td>
<td>HDAC inhibitors</td>
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<tr>
<td>Atezolizumab (PD-L*(1)</td>
<td>ACY-241&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Durvalumab (PD-L(1)</td>
<td>Ricolinostat</td>
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<tr>
<td>Nivolumab (PD-(1)</td>
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HDAC, histone deacetylase.

Novel Therapies to Watch For (cont)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agents</th>
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<tbody>
<tr>
<td>SINE XPO1 antagonists</td>
<td>KPT-8602¹</td>
</tr>
<tr>
<td>AKT inhibitor</td>
<td>GSK2141795²</td>
</tr>
<tr>
<td>MEK1/2 inhibitor</td>
<td>Trametinib²,³</td>
</tr>
<tr>
<td>KSP inhibitors</td>
<td>Filanesib (ARRY-520)⁴</td>
</tr>
<tr>
<td>BTK inhibitors</td>
<td>Ibrutinib*, AVL-292</td>
</tr>
<tr>
<td>CDK inhibitors</td>
<td>PD0332991*, SCH727965, AT*7519</td>
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<tr>
<td>HSP90 inhibitors</td>
<td>Ganetespiib (STA-*(9090)</td>
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<tr>
<td>FGFR3 inhibitor/antibodies</td>
<td>TKI258*, MFGR1877S</td>
</tr>
<tr>
<td>Mutant B-Raf inhibitor</td>
<td>Vemurafenib</td>
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MGUS ➔ EMG

- Essential Monoclonal Gammopathy:
- Presence of serum or urine Immunoglobulin (Ig) or Light Chain (LC) in the absence of B-cell tumor (e.g. B-cell Lymphoma, WSM, MM, Plasmacytoma, Amyloidosis) or even Solid Tumors (like Gastric Ca, or Breast Ca)
- MGUS is less appropriate since the significance of MG is now determined (>90% of MM cases arise from MGUS)
  - IgG and IgA MGUS ➔ MM, or Amyloidosis
  - IgM MGUS ➔ WSM, or Lymphoma
Multiple Myeloma; Current Update

- MGUS $\rightarrow$ Essential Monoclonal Gammopathy (EMG)
- Multiple Myeloma (MM) & Plasma Cell Leukemia (PCL)
- Macroglobulinemia (WSM) & Lymphoplasmacytic Lymphoma (LPL) which are MYD 88 $^+$ by molecular techniques
- Light Chain Disease (LCD)
- Heavy Chain Disease (HCD)
- Amyloidosis (ALA)
- EMG, MM & PCL, WSM & LPL, LCD, HCD, ALA
Plasma Cell Dyscrasia (PCD)

- PCD is a multifaceted Disease. It is very important to screen for essential monoclonal gammaopathy (EMG) of known significance rather than the old misnomer MGUS.

- Conclusion: the screening for EMG is by measuring Serum and Urine Immunoglobulin (Ig) level and serum & urine Free Light Chain (FLC) in functional and coincidental abnormalities associated with EMG.

- Looking for tissues plasmacytomas and monoclonal plasmacytosis in BM is also important.
KFSHRC Jeddah Branch Experience

- **Treatment Protocols:**

- Due to limited options of the newly approved medication for Multiple Myeloma (MM) we have a fixed protocol that we have been using and we are in process of evaluating the outcome of this successful protocols.

- For Transplant Candidate: Our Induction Protocol is VCD 4-6 cycles with mid and post treatment evaluation followed by stem cell collection if the patient is in remission or VGPR or even partial response sometimes.
KFSHRC Jeddah Branch Experience

• Stem cell collection is GCSF based and not any more Cyclophosphamide based we rarely may need Stem Cell Factor
• There is no role for consolidation in our institution since the evidence is not strong enough
• All patients will go on maintenance Velcade + Dexa every two week for 6 months then monthly for 2 years then every three months till disease progression
For patients with relapsed refractory Multiple Myeloma (RRMM) second line therapies will include VRD, KRD, DVD, DRD, and enrolment in Name Patient Program (NPP) for Elutozumab, Ixazomib, Panpinostat, and even check point inhibitors.

Dr. Albeirouti the MM Site leader is communicating with the drug companies regarding this matter.
KFSHRC Jeddah Branch Experience

- For non-transplant Candidate: Same induction with VCD 4-6 Cycles with mid and post treatment evaluation and if the patient is in remission or VGPR then maintenance using MPV (or MDV) monthly for 2 years then every three months till diseases progression.

- Due to limited access to IMID in our institution we will not use them here, keeping in mind that our institution does not accept non-transplant candidates but sometimes comorbidities or patient refusal of the transplant might dictate this approach.
KFSHRC Jeddah Branch Experience

- Supportive care for patients with MM:
- IVIg 0.4g/kg monthly for patients with recurrent bacterial infection of the lung and sinuses
- VTE Prophylaxis will use Enoxaparin 40 mg SC Daily for high risk patients and low dose aspirin in low risk patients with caution
PCD & Multiple Myeloma; The Multifaceted Disease

Immunotherapy
The Changing Paradigm of Medicine

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*Williams Manual of Hematology 9th ed. 2017*
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**EMG, MM & PCL, WSM & LPL, LCD, HCD, ALA**
MGUS \rightarrow EMG

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- Presence of serum or urine Immunoglobulin (Ig) or Light Chain (LC) in the absence of B-cell tumor (e.g. B-cell Lymphoma, WSM, MM, Plasmacytoma, Amyloidosis) or even *Solid Tumors* (like Gastric Ca, or Breast Ca)
- MGUS is less appropriate since the significance of MG is now determined (>90% of MM cases arise from MGUS)
  - IgG and IgA MGUS \rightarrow MM, or Amyloidosis
  - IgM MGUS \rightarrow WSM, or Lymphoma
Functional Abnormalities Associated with EMG

- Also EMG is associated with functional abnormalities that are pertinent to internal medicine and family medicine like:
  - Hematological;
    - Anti RBC Abs (DCT+ve),
    - Acquired VWD (Prolonget aPTT),
    - Immune Neutropenia,
    - Cryoglobulinemia,
    - Cryofibringenemia,
    - Dysfibrogeniemia,
    - Acquired C1 esterase deficiency (Angioedema),
    - Acquired antithrombin (Thrombosis),
    - Anti-Phospholipid Ab (APS)
    - Deep Vein Thrombosis
  - Also Nephropathy, Neuropathy, Oculopathy, Endocrinepathy, etc.
Functional Abnormalities Associated with EMG Cont.

- Nephropathy
  - Acquired Fanconi Renal Disease
- Neuropathy
  - Antiacetylcholine receptor Ab
- Oculopathy
  - Corneal Keratopathy
  - Exaggerated Copper Binding (Pseudo-Kayser-Fisher Corneal Rings) → visual impairment
- Endocrinepathy
  - Insulin Ab
Neuropathies Associated with EMG

- 4% of patients with EMG → have Neuropathy
- 10% of patients with Neuropathy → have EMG
- IgM → Dysesthesias of hands and feet, loss of vibration and position sense, ataxia, intention tremor, atrophy of distal muscle groups
- IgG & IgA → Chronic Inflammatory Demyelinating Neuropathy, or sensory axonal, or mixed neuropathy of different severity, with remitting or progressive course
- IgA → Dysautonomia
Neuropathies Associated with EMG

- Treatment:
  - Intra Venous Immunoglobulin IgG (IVIg)
  - Glucocorticosteroid
  - Immunoabsorption with Staph Protein A
  - Plasma Exchange or Plasmapheresis
  - Immune Suppressive Cytotoxic Chemotherapy
  - Rituximab
  - HDC with ABMT
Coincidental Disorders Associated with EMG

- Carcinomas:
  - Colon, Lung, Prostate, *Gastric, Breast*
- Myeloid Malignancies:
  - MPN: CML, CNL, PRV
  - AML
- Lymphoid Malignancies:
  - Hodgkin’s Lymphoma
  - T-cell Lymphoma
- After Chemotherapy, Radiotherapy, etc.
- After Bone Marrow, Kidney, Liver Transplantation
- Systemic Capillary Leak Syndrome (CLS)
Coincidental Disorders Associated with EMG

- Connective Tissue Disease:
  - SLE
  - RA
  - Scleroderma
  - Sjogren disease
  - Polymyalgia Rheumatica
  - Psoriatic Arthritis
Coincidental Disorders Associated with EMG

- Autoimmune Disease:
  - Crohn Disease
  - Hashimoto thyroiditis
  - Myasthenia Gravis

- Cutaneous Diseases:
  - Schnitzler syndrome
  - Urticaria
  - Hyperkeratosis spicules
  - Pyoderma Gangrenosum (Neutrophilic Dermatoses)
  - Psoriasis
  - Scleromyxedema
Coincidental Disorders Associated with EMG

- **Endocrine Diseases:**
  - Hyperparathyroidism
  - Pituitary Adenoma
  - Hyperlipidemia

- **Hepatic Diseases:**
  - Cirrhosis
  - Hepatitis

- **Ocular Disease:**
  - Corneal Gammopathy
  - Psudo-Kayser-Fleisher ring
Coincidental Disorders Associated with EMG

- **Bone Diseases:**
  - Osteoporosis
  - Axial Bone Fracture
  - Diffused Idiopathic Skeletal Hyperstosis

- **Infectious Diseases:**
  - Bacterial Endocarditis
  - Corynebacterium Species
  - CMV
  - EBV
  - HIV
  - TB
  - Purpura Fulminans
Coincidental Disorders Associated with EMG

- Obesity has been associated with increased incidence of EMG (and MM)
- Pregnancy
- Inherited Diseases:
  - Gaucher Disease Type I
  - Hereditary Spherocytosis
- Hematologic Diseases:
  - Pernicious Anemia
  - Chronic Neutropenia
  - Cryoglobulinemia
  - Transient Monoclonal or Oligoclonal Gammopathies
  - Vitamin B12 Deficiency
  - Factitious Hyperferremia
- Also Factitious increase in C-reactive protein (CRP)
Treatment, Course, & Prognosis of EMG

- 25% will develop hematological malignancy over a 25 year of observation (Approximately 1% per year will develop B-cell malignancy of MM, ALA, WSM, Lymphoma, CLL, etc.)
- 25% will have a modest increase in immunoglobulin protein but will not progress to a B-cell malignancy
- 50% of patients do not have progression (clonal evolution) during their lifetime
- Rarely the EMG disappears spontaneously
- Therapy is not required unless functional impairment
Multiple Myeloma; Current Update

- MGUS → Essential Monoclonal Gammopathy (EMG)
- Multiple Myeloma (MM) & PCL
- Macroglobulinemia (WSM) & LPL
- Light Chain Disease (LCD)
- Heavy Chain Disease (HCD)
- Amyloidosis (ALA)

- EMG, MM & PCL, WSM & LPL, LCD, HCD, ALA
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**EMG, MM & PCL, WSM & LPL, LCD, HCD, ALA**
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Thanks