Case 1 – History

- 45F was in her usual state of good health until she developed an ear infection. She received antibiotics for this but noticed ongoing low grade fevers and also bruising.
- PMH/PSH: hypothyroidism
- SH: married, 2 kids, stay at home mom, never smoker
- Physical exam: well-appearing, bruising on arms and legs, no LAD, no hepatosplenomegaly, neurologic exam grossly normal

Case 1 – Labs

<table>
<thead>
<tr>
<th>Lab</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>73</td>
<td>K/µL</td>
</tr>
<tr>
<td>Hgb</td>
<td>8.0</td>
<td>g/dL</td>
</tr>
<tr>
<td>Hct</td>
<td>23.9</td>
<td>%</td>
</tr>
<tr>
<td>Plt</td>
<td>42</td>
<td>K/µL</td>
</tr>
<tr>
<td>WBC differential:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blasts</td>
<td>93.9</td>
<td>%</td>
</tr>
</tbody>
</table>

Case 1 – Labs

<table>
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<tr>
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<td>WBC differential:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blasts</td>
<td>93.9</td>
<td>%</td>
</tr>
</tbody>
</table>

Panel Members

- Lloyd Damon, MD – Professor of Medicine, UCSF
- Jason Gotlib, MD, MS – Professor of Medicine, Stanford
- Michael Green, MD – Kaiser Permanente, TPGM
- Jarrod Holmes, MD – St. Joseph Health Medical Group
- Brian Jonas, MD, PhD – Assistant Professor of Medicine, UC Davis
- Michaela Liedtke, MD – Associate Professor of Medicine, Stanford
- Aaron Rosenberg, MD, MS – Assistant Professor of Medicine, UC Davis
- Shahzad Siddique, MD – Mercy Medical Group
- Li-Wen Huang, MD – fellow, UCSF
Case 1 – Work-Up

- Bone marrow biopsy showed AML with 90% blasts
  - Immunophenotype CD11c, CD33, CD56 partial, CD64, CD117, MPO+
  - Normal cytogenetics
  - FISH negative for del(5q), monosomy 5, del(7q), monosomy 7, trisomy 8, t(8;21), t(15;17), del(20q), CBF8 rearrangement, MLL rearrangement
  - Molecular diagnostics: NPM1+, FLT3 ITD+. Mutant allele ratio 0.3. No evidence of FLT3 TKD, IDH1/2, CEBPA.
- LVEF was 65%

Case 1

What is her risk status based on cytogenetics and molecular abnormalities?

- A. Favorable
- B. Intermediate
- C. Poor
- D. It’s complicated

NCCN Guidelines Version 1.2019
Acute Myeloid Leukemia

European LeukemiaNet Risk Stratification by Genetics in Non-APL AML

Risk Category | Genetic Abnormality
--- | ---
Favorable | Mutated NPM1 without FLT3/ITD or with FLT3/ITD<sup>−</sup>
Intermediate | Mutated NPM1 or FLT3/ITD<sup>−</sup> with adverse risk genetics (t(15;17), t(8;21), t(11;19), 8q24, 9p21, 7p15, 11p15.5)
Poor/Adverse | Complex karyotype, MLL rearrangement, t(8;21), t(15;17), monosomy 7, del(7q), monosomy 5, del(5q), del(7q), del(20q)

Case 1 – NPM1+ & FLT3-ITD<sub>low</sub> controversy

Multidisciplinary Management of Cancers: A Case-based Approach

Case – Initial Treatment

- She started treatment with 7+3 + midostaurin.
- Nadir bone marrow biopsy showed no evidence of leukemia, and marked hypoplasia.
- Her counts recovered with residual anemia Hb 8-9. She had a repeat bone marrow biopsy which showed remission.

Case 1 – Post-Remission Therapy

- Did not recommend allogeneic stem cell transplantation at CR1 based on ELN and NCCN classifications of favorable risk.
- Confirmed MRD-negative CR by NPM1 quantitative PCR
- HiDAC + midostaurin on D8-21 x 4 cycles, followed by midostaurin maintenance x 12 mo per the RATIFY trial

Case 1 – Relapse

- 13 months later she returns with relapsed disease.
- Bone marrow biopsy results are similar:
  - Immunophenotype CD11c, CD56 partial, CD64, CD117, MPO+. CD33-
  - Normal cytogenetics
  - AML FISH negative
  - Molecular diagnostics: NPM1+, FLT3 ITD+. No evidence of FLT3 TKD, IDH1/2, CEBPA.
19th Multidisciplinary Management of Cancers: A Case-based Approach

Case 1
What would you treat her with?

A. Other salvage chemotherapy (FLAG-IDA, MEC, etc)
B. HMA
C. Gemtuzumab ozogamicin
D. Gilteritinib

19th Multidisciplinary Management of Cancers: A Case-based Approach

Case 1 – FLT3+ AML Take Home Points

- NPM1+ and FLT3 ITD with low allelic ratio (<0.5), previously considered poor risk due to the FLT3 ITD, may be favorable risk and may not necessarily need allogeneic transplant. This is reflected in ELN and NCCN guidelines
- Many FLT3 assays don’t include the allelic ratio – may need to be ordered specifically
- Based on the RATIFY study, midostaurin should be continued as maintenance for a total of 12 months
- FLT3 inhibitor gilteritinib can be used as monotherapy for R/R FLT3+ AML
- Be on the look out for data on quizartinib

19th Multidisciplinary Management of Cancers: A Case-based Approach

Case 1 – Relapse

- Gilteritinib was FDA-approved 11/2018 for FLT3+ AML (ITD & TKD) based on ADMIRAL study (NCT02014558):
  - CR/CRh 21% (n = 29; 95% CI 14.5-28.8) at a median follow-up of 4.6 mo
  - Fewer, milder side effects than typically seen with salvage chemo
  - Final analysis pending
- Quizartinib was granted FDA priority review based on results of the QuANTUM-R study (NCT02039726):
  - Median OS 6.2 mo vs 4.7 mo with salvage chemo (HR 0.76; p=0.0177)

End of Case 1
Case 2 – History

- 83F presented with a few weeks of generalized weakness, decreased appetite, productive cough x5d, pleuritic chest pain.
- PMH/PSH: hypothyroidism, partial thyroidectomy, total knee replacements
- Physical Exam notable for:
  - O2 sat mid 90s on 1-2L O2
  - ECOG 2
  - Bibasilar crackles and wheezes. 1+ edema bilaterally.

Case 2 – Labs

<table>
<thead>
<tr>
<th>Lab</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>107</td>
<td>K/µL</td>
</tr>
<tr>
<td>Hgb</td>
<td>10.2</td>
<td>g/dL</td>
</tr>
<tr>
<td>Hct</td>
<td>33.5</td>
<td>%</td>
</tr>
<tr>
<td>Plt</td>
<td>213</td>
<td>K/µL</td>
</tr>
<tr>
<td>WBC differential</td>
<td>26</td>
<td>%</td>
</tr>
</tbody>
</table>

- CXR: bibasilar opacities, superimposed interstitial edema
- RVP: +metapneumovirus

Case 2 – Work-Up

- Bone marrow biopsy showed AML with 20% blasts
  - Immunophenotype: +CD13, slightly weak CD33, CD34, CD38, CD71, CD117, CD123, HLA-DR with a subset co-expressing CD7, weak-variable MPO
  - Normal cytogenetics
  - AML FISH negative
  - Molecular diagnostics: +IDH1, SRSF2, DNMT3A. No evidence of IDH2, FLT3 ITD/TKD, NPM1, CEBPA.

Case 2

What would you treat her with?

A. HMA
B. HMA + venetoclax
C. Ivosidenib
D. LDAC + glasdegib
E. Any of the above
Case 2 – Initial Treatment

- Started on hydroxyurea for cytoreduction, allopurinol + hydration for TLS ppx
- Treated for community-acquired PNA with ceftriaxone and azithromycin
-Started 7-day azacitidine with venetoclax 100mg (with concurrent vori + levo)

Table 7. Management of Potential VENCLEXTA Interactions with CV/P3A and Pgp Inhibitors

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>Initiation and Ramp-Up Phase</th>
<th>Steady Daily Dose (After Ramp-Up Phase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venetoclax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>Day 1 – 10 mg</td>
<td>Reduce VENCLEXTA dose to 50 mg.</td>
</tr>
<tr>
<td></td>
<td>Day 2 – 50 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 3 – 90 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 4 – 90 mg</td>
<td></td>
</tr>
<tr>
<td>5-Aminoimidazoles</td>
<td>Comorbid conditions</td>
<td>Control VENCLEXTA dose to 100 mg.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Case 2 – Venetoclax adjustments for toxicity

- For patients in CRi or MLFS at end of cycle 1, and persistent neutropenia after completion of the assessment period for dose-limiting toxicities, venetoclax could be interrupted to allow neutrophil recovery to ≥500 cells/μL before initiation of the next cycle. Decitabine or azacitidine was also delayed.

Case 2

On cycle 2 day 1, you note cytopenias: WBC 1.0 (ANC 0.3), Hgb 9, platelets... A bone marrow biopsy is performed which shows hypocellular marrow (20%) with <5% blasts. What should you do?

A. Hold aza + venetoclax until cytopenias resolve
B. Proceed with C2 aza + venetoclax
C. Switch to 5-day azacitidine
D. Dose reduce venetoclax

Case 2

Venetoclax adjustments for toxicity

- Bone marrow biopsy at the end of cycle 2 showed hypercellular marrow; blasts not increased (2%). Results favored to be bone marrow in recovery.
- Due to prolonged nadirs, regimen eventually modified to:
  - Azacitidine x5 days instead of 7
  - Venetoclax 100mg daily on D1-14 of 28 day cycle
If this patient relapses, what would you treat her with?

A. Gemtuzumab ozogamicin
B. Enasidenib
C. Ivosidenib
D. LDAC + glasdegib
E. Hospice

Case 2 – IDH1/2 inhibitors

- Ivosidenib (IDH1 inhibitor) FDA approved 7/2018 for R/R IDH1 mutated AML
  - ORR 41.6%, median time to response 1.9 months (0.8-4.7)
- Enasidenib (IDH2 inhibitor) FDA approved 8/2017 for R/R IDH2 mutated AML
  - ORR 40.3%, median time to response 1.9 months (range 0.5-9.4)

Case 2 – Take Home Points

- Lots of new lower intensity options for AML approved in last few years
  (HMA+venetoclax, LDAC+venetoclax, enasidenib, ivosidenib, glasdegib)
- Response assessment with aza+ven is sooner than with aza alone. For patients with CRI or MLFS consider holding therapy.
- Venetoclax requires cytoreduction if WBC>25, TLS ppx, dose modifications for drug interactions (azoles, other CYP3A inhibitors)
- IDH1/2 inhibitors good options for relapse/refractory IDH1/2-mutated AML
**Case 3 – History**

- 70M with atrial fibrillation (s/p ablation x1, recent cardioversion in NSR on apixaban), HTN, stage 3b CKD, OSA, osteoarthritis
- 10 years ago – noted to have platelets 100-140s
- 4 years ago – developed lymphocytosis (WBC 17, ALC 10) with normal H&H and platelets 110
  - Diagnosed with CLL (FISH +del 13q14, IGVH unmutated, CD38 neg)
  - Mild splenomegaly noted on CT scan
- Monitored without treatment

**Case 3 – Labs**

Now presents with night sweats, prominent cervical LNs.

4 years ago:

<table>
<thead>
<tr>
<th>Lab Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>15.6</td>
</tr>
<tr>
<td>Hgb</td>
<td>14.1 g/dL</td>
</tr>
<tr>
<td>Hct</td>
<td>41.8 %</td>
</tr>
<tr>
<td>Plt</td>
<td>117 K/µL</td>
</tr>
<tr>
<td>WBC differential</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC</td>
<td>6.6 K/µL</td>
</tr>
<tr>
<td>ALC</td>
<td>10.3 K/µL</td>
</tr>
</tbody>
</table>

On presentation now:

<table>
<thead>
<tr>
<th>Lab Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>35.0 K/µL</td>
</tr>
<tr>
<td>Hgb</td>
<td>11.4 g/dL</td>
</tr>
<tr>
<td>Hct</td>
<td>35.6 %</td>
</tr>
<tr>
<td>Plt</td>
<td>50 K/µL</td>
</tr>
<tr>
<td>WBC differential</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC</td>
<td>3.5 K/µL</td>
</tr>
<tr>
<td>ALC</td>
<td>30.6 K/µL</td>
</tr>
</tbody>
</table>

**Case 3 – Initial Treatment**

- Started on ibrutinib 420mg daily for Rai stage IV CLL, progressive thrombocytopenia, constitutional symptoms
- Supported by Alliance study presented at the ASH 2018 Plenary Session
Case 3 – Initial Treatment


A month later presented with fever, cough
CT chest showed multiple pulmonary nodules

Case 3

A. Start levofloxacin
B. Start vanc + zosyn
C. Start treatment dose TMP-SMX
D. Start voriconazole
E. Bronchoscopy

Case 3 – Adverse Effects: Fungal Pneumonia

Case 3

A. Start levofloxacin
B. Start vanc + zosyn
C. Start treatment dose TMP-SMX
D. Start voriconazole
E. Bronchoscopy

Case 3 – Adverse Effects: Fungal Pneumonia

After seeing the CT chest, what do you do now?

A. Start levofloxacin
B. Start vanc + zosyn
C. Start treatment dose TMP-SMX
D. Start voriconazole
E. Bronchoscopy

Bronchoscopy performed
BALs cytology + GMS organism, cell count showed hyphal elements
Bacterial, fungal cultures negative
Negative for respiratory viruses, PJP, CMV, legionella
Treated for fungal pneumonia with voriconazole x 3 months
Ibrutinib dose reduced to 140mg daily while on voriconazole
Case 3 – Adverse Effects: Fungal Pneumonia

- Retrospective analysis of a case series of invasive fungal infections in patients in France taking ibrutinib found:
  - Early onset – median time from ibrutinib initiation of 3 months
  - Invasive aspergillosis over-represented (also crypto, PCP, mucor)
  - High incidence of CNS involvement
  - Other factors that may contribute to infections often associated (neutropenia, corticosteroids, chemotherapy ≤6 months prior to ibrutinib)


Case 3 – Adverse Effects: Afib

- WBC & ALC peaked at 86 & 80, then slowly downtrended over the next 5 months and have now normalized. Lymphadenopathy also resolved.
  - Platelets remain in 70s – thought possibly autoimmune
  - Complains of fatigue, lightheadedness
  - Found to have paroxysmal afib again (30% of the time on zoipatch)
    - H/o ablation and cardioversion before ibrutinib initiation
    - Was in NSR at time of ibrutinib initiation
    - Cardiologist recommends another ablation

Case 3

He asks you if he should pursue another ablation. What do you suggest?

A. Dose reduce ibrutinib
B. Continue full dose ibrutinib and pursue afib ablation
C. Stop ibrutinib and observe, initiating therapy at time of progression
D. Switch to venetoclax
E. All of the above

His symptoms and afib burden persisted despite a lower dose of ibrutinib
- After discussion with the patient, the decision was made to discontinue ibrutinib and monitor
- Repeat holter monitor off ibrutinib showed no arrhythmia burden. Did not require 2nd ablation
Although ibrutinib is generally well tolerated, it is still associated with adverse events, especially in older patients.

**Case 3 – 2nd line therapy**

- He was started on venetoclax 20mg daily, with weekly dose ramp-up over 5 weeks to reach goal 400mg daily

**Table 1. Dosing Schedule for Ramp-Up Phase in Patients with CLL/NLL**

<table>
<thead>
<tr>
<th>VENCLEXTA Daily Dose</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 1</strong></td>
<td>20 mg</td>
</tr>
<tr>
<td><strong>Week 2</strong></td>
<td>50 mg</td>
</tr>
<tr>
<td><strong>Week 3</strong></td>
<td>100 mg</td>
</tr>
<tr>
<td><strong>Week 4</strong></td>
<td>200 mg</td>
</tr>
<tr>
<td><strong>Week 5 and beyond</strong></td>
<td>400 mg</td>
</tr>
</tbody>
</table>

- TLS prophylaxis and monitoring recommendations based on tumor burden (see NCCN)

**Case 3**

6 months after stopping ibrutinib, he presents with fatigue, night sweats, symptomatic splenomegaly, LAD. What do you do?

A. Resume ibrutinib
B. Start acalabrutinib
C. Start venetoclax
D. Start idelalisib + rituximab
E. Start duvelisib

- Continues to have persistent fatigue, splenomegaly, LAD
- Platelets now 20-30s, although Hgb and WBC/ANC are normal
  - Recall his baseline platelets are 100s prior to treatment
  - Even while responding to ibrutinib platelets remained in the 70s
- He needs a hip replacement and lung biopsy to evaluate possible lung cancer, but cannot get procedures unless his platelets are >50
Case 3 – Thrombocytopenia

- BMBx was obtained which showed only 20% involvement with CLL
- Venetoclax was held temporarily, with no improvement in platelet count
- Thrombocytopenia thought to be more likely related to CLL-related ITP +/- splenic sequestration
- Recommended adding rituximab to venetoclax
  - Effective regimen for CLL given only partial response to venetoclax
  - Rituximab may be helpful for ITP as well

Case 3

- Other management for suspected ITP
  - Transfused 2 units of platelets for procedure but platelets remained 40s
  - IVIG x1 with no effect
  - Opted to avoid prolonged steroids 2/2 h/o fungal PNA
  - Started Promacta 75mg daily
  - After continued promacta, his platelets improved to 50-60s
  - His fatigue, splenomegaly, LAD persisted despite treatment with venetoclax + rituximab

He asks about changing therapy. What do you recommend?

A. Continue venetoclax + rituximab
B. Ibrutinib
C. Acalabrutinib
D. Idelalisib + rituximab
E. Duvelisib
Case 3 – Subsequent Therapy

- He was started back on ibrutinib
  - Constitutional symptoms, LAD and splenomegaly all improved
  - Platelets stable/slightly improved at 50-80s
- However, 2 months later he had recurrent afib, so ibrutinib was stopped
- Switched to acalabrutinib
  - No recurrent episodes of afib to date
  - Platelets 100-130s

Case 3 – 2nd generation BTK inhibitors

- Second generation BTK inhibitors such as acalabrutinib are generally more BTK-selective, which may improve the safety profile and/or efficacy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical results</th>
<th>Common/important side effects</th>
<th>Off target kinase inhibited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib [16,22,23]</td>
<td>Relapsed/refract: ORR 63%-91%, median PFS NR (3+ years)</td>
<td>Dianhe, arthralgia, hypertension, atrial fibrillation, bleeding</td>
<td>Tec, EGFR, JAK3, ERBB2, ERBB4, ITK</td>
</tr>
<tr>
<td>Acalabrutinib [37]</td>
<td>Relapsed/refract phase II: ORR 95% (PR 85%, PRi 10%), PFS 98% at median F/U of 14.3 mo.</td>
<td>Headache, dianhe, weight gain, hypertension,</td>
<td>ERBB4</td>
</tr>
</tbody>
</table>

Case 3 – Take Home Points

- Ibrutinib should be offered to older adults with IGVH unmutated CLL
- Although ibrutinib is generally better tolerated than chemoimmunotherapy, it requires indefinite therapy and can be associated with adverse effects including fungal pneumonias, afib, hemorrhage, etc that can result in treatment interruption or discontinuation
- 2nd generation BTKi may be associated with fewer side effects
- Potential causes for thrombocytopenia in a CLL patient include disease, drug, immune-mediated, splenic sequestration
19th Multidisciplinary Management of Cancers: A Case-based Approach

Case 4

At OSH:
• 61 year old with moderate fatigue, abdominal fullness, and weight loss x 20 lb x 6 mo
• Hepatosplenomegaly on exam; on CT: spleen 23 cm; liver 27 cm (craniocaudal)
• CBC: WBC 8.9 x 10^9/L, Hb 13.1 g/dL, and platelet count 140 x 10^9/L.
  • Diff: Neutrophils 34%, lymphocytes 12%, monocytes 45% (AMC 4270)
• Peripheral smear: increased number of monocytes with promonocytic forms. No blasts. Leukocytes with hypolobation and pseudo Pelger-Huet morphology
• Alkaline phosphatase increased to 280 IU/L (nl < 130)

19th Multidisciplinary Management of Cancers: A Case-based Approach

Case 4

Which of the following tests would you order to further clarify the diagnosis?

A. FISH for the CHIC2 deletion (FIP1L1-PDGFRα)
B. FISH for PDGFRB
C. FISH for FGFR1
D. KIT D816V by allele-specific PCR and serum tryptase level
E. JAK2 V617F

19th Multidisciplinary Management of Cancers: A Case-based Approach

Case 4

• The patient is positive for KIT D816V with an allele burden of 35%
• A myeloid mutation panel also shows pathogenic mutations in SRSF2, TET2, and ASXL1.
• The serum tryptase level is 215 ng/ml (normal < 11.4 ng/ml)
Case 4

What is the patient’s diagnosis?

A. Chronic myelomonocytic leukemia (CMML)-1
B. Indolent systemic mastocytosis (ISM)
C. SM-CMML-1 (systemic mastocytosis with an associated hematologic neoplasm (SM-AHN) )
D. MDS/MPN-unclassifiable (MDS/MPN-U)

WHO Diagnostic Criteria for Systemic Mastocytosis

**Major**
- Mast cell aggregates (≥ 15) in the marrow or other extracutaneous tissue

**Minor**
- Spindle-shaped mast cells
- KIT D816V or other activating KIT mutation
- CD25 +/- CD2 expression on mast cells
- Serum tryptase > 20 ng/mL

Diagnosis requires: 1 major + 1 minor or > 3 minor criteria)

**Advanced SM**

- >20% mast cells on BM aspirate

SM with an Associated Hematologic Neoplasm (SM-AHN)

- It is challenging to determine whether organ damage is related to the SM or AHN component; organ-directed biopsy may be helpful
- KIT D816V may be shared by mast cells and AHN-derived cells (e.g. monocytes in CMML) 

Heterogeneous extent and severity of SM-related organ involvement:

- **B Findings** (Higher Burden Disease)
  1. BM: >30% mast cells AND tryptase level >200 ng/ml
  2. Hepatomegaly or splenomegaly without liver dysfunction or hyperplenism; or lymphadenopathy (> 2cm)
  3. Signs of dysplasia or myeloproliferation, without a frank AHN; normal or mildly abnormal blood counts

- **C Findings** (Organ Damage) (Need for Cytoreduction)
  1. Cytopenias due to BM infiltration
  2. Liver dysfunction, ascites, and/or portal hypertension
  3. Large osteolytic and/or pathologic fractures
  4. Puffy spleenomegaly with hypersplenism
  5. Malabsorption (hypoalbuminemia) with weight loss due to GI mast cell infiltrates

Neoplastic mast cells are not equal opportunity organ offenders
- e.g. low marrow burden but severe liver disease in the same patient

**ISM**

- 0 or 1 B-findings

**SSM**

- ≥ 2 B-findings

**ASM**

- ≥ 2 C-findings

**SM with an Associated Hematologic Neoplasm (SM-AHN)**

- A large burden of mast cells can mask signs of an AHN in the marrow (e.g. MCL masking dysplasia)
- Conversely, SM may lurk in the shadows of an AHN (e.g. unmasking of mast cell aggregates in a hypoplastic marrow after chemotherapy for AML)

- It is challenging to determine whether organ damage is related to the SM or AHN component; organ-directed biopsy may be helpful
- KIT D816V may be shared by mast cells and AHN-derived cells (e.g. monocytes in CMML) 

**SM, MDS, AML, MPN**

- Systemic Mastocytosis: ~90% of cases

**Hone et al, J Clin Oncol, 2010**

**Sotlar et al, J Pathol, 2010**
Heterogeneity in SM-AHN:
Overall Survival (OS) Depends on AHN Subtype

Rates of leukemic progression
(overall 13%)

19th Multidisciplinary Management of Cancers: A Case-based Approach

Case 4

What treatment would you now consider for this patient?

A. Decitabine
B. Imatinib
C. Cladribine
D. PEG-IFN-α
E. Midostaurin or clinical trial with selective KIT D816V inhibitor (e.g. avapritinib)

19th Multidisciplinary Management of Cancers: A Case-based Approach

Case 4

What treatment would you now consider for this patient?

A. Decitabine
B. Imatinib
C. Cladribine
D. PEG-IFN-α
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19th Multidisciplinary Management of Cancers: A Case-based Approach

Case 4

What treatment would you now consider for this patient?

A. Decitabine
B. Imatinib
C. Cladribine
D. PEG-IFN-α
E. Midostaurin or clinical trial with selective KIT D816V inhibitor (e.g. avapritinib)
Phase I: Avapritinib: Reduction in Measures of Mast Cell Burden

19th Multidisciplinary Management of Cancers: A Case-based Approach

Case 4

After doing well for 24 months on study, the patient develops changes in the blood counts: WBC count increased from normal to $28 \times 10^9/L$, Hb 11.7 to 8.4 g/dL, and platelets 130 to $72 \times 10^9/L$. Diff: increased myeloid immaturity with 35% monocytes and 7% blasts.

A repeat marrow shows stable low mast cell count <5%; however the myeloblast count has increased from 8% to 16%.

Tryptase level is stable at 15 ng/ml; albumin 4.5 mg/dL; alkaline phosphatase normal.

19th Multidisciplinary Management of Cancers: A Case-based Approach

What treatment should be considered at this time?

A. Hypomethylating agent (HMA; e.g. azacitidine or decitabine)
B. HMA + venetoclax
C. HMA + midostaurin
D. Allogeneic stem cell transplantation
E. Induction chemotherapy

Overall survival (OS) at 3 years: 57%
- 76% for SM-AHN
- 43% for ASM
- 17% for MCL

Adverse factors for OS:
- MCL
- RIC vs. myeloablative
Key Points

• If you don’t think about mast cell disease, you won’t diagnose it; expert pathology evaluation and appropriate marrow staining is critical
• Initial treatment decision making: does the patient need more immediate treatment for the SM component or the AHN component?
• KIT inhibitors can be very effective against the SM component; utility against the AHN is variable; progression of the AHN is a not uncommon cause of disease transformation and usually drives prognosis
• In higher risk CMML, HMA may be used as a bridge for allo-HCT; the latter should be considered if the patient is suitable and a donor option is available

Case 5 – History

- 75M otherwise healthy presents with new back pain and fatigue
- X-ray shows multiple compression fracture at L4 and L5

<table>
<thead>
<tr>
<th>Lab</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb</td>
<td>9.5</td>
<td>g/dL</td>
</tr>
<tr>
<td>Cr</td>
<td>1.2</td>
<td>mg/dL</td>
</tr>
<tr>
<td>Ca</td>
<td>10.6</td>
<td>mg/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.7</td>
<td>g/dL</td>
</tr>
<tr>
<td>LDH</td>
<td>250</td>
<td>U/L</td>
</tr>
<tr>
<td>β2-microglobulin</td>
<td>3.8</td>
<td>µg/mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein</td>
<td>11</td>
<td>g/dL</td>
</tr>
<tr>
<td>SPEP</td>
<td>M-protein 4.2</td>
<td>g/dL</td>
</tr>
<tr>
<td>IFE</td>
<td>IgG kappa</td>
<td></td>
</tr>
<tr>
<td>LLC</td>
<td>5</td>
<td>mg/L</td>
</tr>
<tr>
<td>K/L ratio</td>
<td>240</td>
<td></td>
</tr>
</tbody>
</table>

Imaging:
- PET/CT scan with multiple hypermetabolic lytic lesions
- No extramedullary disease noted
- Bone marrow biopsy
  - 75% kappa-restricted plasma cells
  - FISH: t(11;14)
Case 5
What is the ISS and Revised-ISS stage?
A. II and III
B. III and III
C. II and II
D. III and II
E. I and II

- ISS: requires B2M and Alb
  - I: Alb ≥3.5 g/dL, B2M <3.5 mg/L
  - II: neither ISS I nor III
  - III: B2M >5.5mg/L
- Revised-ISS: requires B2M, Alb, LDH, iFish
  - I (n=871): ISS I & nl LDH, iFish
  - II (n=1894): neither R-ISS I nor III
  - III (n=295): ISS III plus either
    - High LDH (>nl)
    - 1 of t(4, 14), t(14, 16), or 17p


Case 5 – IMWG International Staging System

Case 5 – Trial results for transplant ineligible NDMM

- SWOG S0777: RVd vs Rd
  | | | |
  | VRd (n = 242) | Rd (n = 229) | HR | P Value |
  | Median PFS (mo) | NR (60% - 30) | 19.1 | 0.43 |
  | Median OS (mo) | 75 | 64 | 0.025 |

- ALCYONE trial: Dara-VMP vs VMP
  | | | |
  | Dara-VMP (n = 350) | VMP (n = 356) | HR | P Value |
  | Median PFS (mo) | NR (60% - 30) | 19.1 | 0.43 |
  | ORR | 91 % | 74 % | <0.0001 |

OS stratified by Revised-ISS
Case 5 – MAIA study (ASH 2018)

• Phase 3 study of Dara-Rd vs Rd in transplant ineligible NDMM (n = 737)
  - PFS improved for D-Rd (not reached) vs Rd (31.9 months)
  - No new safety signals


• D-Rd induced deeper responses and higher rates of MRD negativity

ORR = 81%
ORR = 93%
≥CR: 48%
≥VGPR: 79%
fCR: 25%
fVGPR: 53%


Case 3

The patient achieved VGPR after RVd x 6 cycles. Would you switch to maintenance therapy and if yes with what agent(s)?

A. Continue RVd
B. Continue Rd
C. R single agent
D. Ixazomib
E. No maintenance

Case 5 – Continuous/Maintenance Therapy

Transplant ineligible: FIRST study
Rd18 vs Rd continuous vs MPT

Improved PFS for Rd continuous

Transplant ineligible: MM-015 study
MPR-R vs MPR vs MP

Benboubker et al. NEJM 2014; 371:906-917.
**Case 5 – “Real-world” Phase 3 RCT (ASH 2018)**

- Rd-R vs continuous Rd in elderly and intermediate-fit NDMM
  - Rd x 9 cycles + R maintenance vs continuous Rd, both until PD/intolerance
  - Comparable efficacy
  - Improved tolerability of Rd-R vs continuous Rd

![Image](https://ash.confex.com/ash/2018/webprogram/Paper111796.html)

**Case 5 – TOURMALINE-MM3 study (ASH 2018)**

- Drug change Rd-R
  - Dose reduction 33% vs 43%
  - Withdrawal 19% vs 23%
  - Grade 3+ tox 31% vs 39%

![Image](https://ash.confex.com/ash/2018/webprogram/Paper112079.html)

**Case 5 – TOURMALINE-MM3 study (ASH 2018)**

- Ixazomib maintenance for 24 months significantly improved PFS by 39%
  - Ixazomib was well tolerated; low discontinuation rate, low incidence of SPMs
  - European trial
  - Most patients did not receive IMiD/PI combination for induction
  - No comparative data with standard lenalidomide maintenance

![Image](https://ash.confex.com/ash/2018/webprogram/Paper112079.html)

**Case 5 – RELAPSE**

- He received maintenance therapy with lenalidomide 10 mg for 21/28 days
  - After 2 years of maintenance, he asks for a treatment holiday and goes on a trip. Three months later he has new onset upper back pain and fatigue.
  - Labs: Hgb 10.2 g/dL (rest of the labs fairly normal)
  - PET/CT scan with several new lytic bone lesions, no pathological fractures
  - Bone marrow biopsy
    - 60% kappa-restricted plasma cells
    - FISH still shows t(11;14)
Case 5 – Relapsed/Refractory Disease

<table>
<thead>
<tr>
<th>IMiDs</th>
<th>Proteasome Inhibitors</th>
<th>Monoclonal Abs</th>
<th>HDAC-inhibitor</th>
<th>BCL-2 inhibitor</th>
<th>EPOD-inhibitor</th>
<th>Anti-BCMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td>Bortezomib</td>
<td>Daratumumab</td>
<td>Panobinostat</td>
<td>Venetoclax</td>
<td>Selinexor</td>
<td>AMG 420</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Carfilzomib</td>
<td>Ectizumab</td>
<td>Isatuximab</td>
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<tr>
<td>Pomalidomide</td>
<td>Ixazomib</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Absolozumab</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(Anti-PD-L1 Ab)</td>
</tr>
</tbody>
</table>


Case 5 – Relapsed/Refractory Disease

**Case 5 – Relapsed/Refractory Disease**

- >10 Randomized Trials – “dealer’s choice”
- **Pollux Study in RRMM**
  - PFS 44.5 m vs Rd 17.5 m

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>Prior Therapies</th>
<th>N</th>
<th>Median/PFS [m]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPIRE</td>
<td>Rd vs Vd</td>
<td>1 to 3</td>
<td>792</td>
<td>26.3 ± 5.6</td>
</tr>
<tr>
<td>CICERO@R</td>
<td>Rd vs Vd</td>
<td>1 to 3</td>
<td>505</td>
<td>18.7 ± 6.4</td>
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<tr>
<td>TOURMALINE AMI@R</td>
<td>Rd vs Vd</td>
<td>1 to 3</td>
<td>722</td>
<td>25.8 ± 6.7</td>
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<tr>
<td>ELONGATEIM1</td>
<td>Rd vs Vd</td>
<td>1 to 3</td>
<td>646</td>
<td>19.4 ± 10.0</td>
</tr>
<tr>
<td>POLLUX</td>
<td>Rd vs Vd</td>
<td>≥ 2</td>
<td>568</td>
<td>&gt;32 ± 16.4</td>
</tr>
</tbody>
</table>


**Phase 2 study of Venetoclax + Carfilzomib and Dexamethasone**

- CR 82% (95% CI 71-90)
- VGPR 14% (95% CI 11-19)
- PR 2% (95% CI 1-5)

**COMMENTS**

- 1. Dimopoulos et al. ASH 2018 abstract #155
- 2. Costa et al. ASH 2018 abstract #303
- 3. Topp et al. ASH 2018 abstract #1010
Case 5 – Relapsed/Refractory Disease

- VenKd has promising efficacy (ORR 79%, ≥ CR 38%) that supports investigation of this combination in RRMM
- Efficacy was observed in patients who were PI refractory (ORR 76%, ≥ CR 43%), IMiD refractory (ORR 77%, ≥ CR 23%), and double refractory (ORR 71%, ≥ CR 29%)
- Encouraging activity in non-t(11;14) patients (ORR, 74%, ≥ CR, 32%)
- t(11;14)+ patients had the highest ORR (100%) and ≥ CR (63%)
- The study is ongoing and expanded with 60 additional patients to further investigate the efficacy of this combination, including response durability

Case 5 – Take Home Points

- New strategies for induction
  - Adding mAbs – triplet and quadruplets
  - Maintenance/continuous therapy is standard (lenalidomide, ixazomib)
- Many new agents for RRMM
  - Triplets are standard
    - Daratumumab combinations appear quite effective
    - Sequencing of agents undefined
  - Novel agents in development (Venetoclax+Kd personalized medicine 100% ORR in t(11;14), BCMA targeted therapy appears promising)