ANCO Hematologic Malignancies Update: Leukemias, Lymphoma & Myeloma

CLINICAL CASES

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Case 1: Patient IM

- ID: 52 yo M with prior history of mycosis fungoides (a cutaneous T cell lymphoma) who was lost to follow up returns with fulminant skin lesions

- HPI:
  - 9/2013: Presented to dermatology with 1 year of dermatitis and total body rash
  - Workup:
    - Skin biopsy confirms diagnosis of mycosis fungoides (MF)
    - Peripheral Blood Flow Cytometry: Minor population of atypical T-cells (0.2% of total events)
    - CT C/A/P with axillary and inguinal lymphadenopathy
    - FNA of inguinal lymph nodes without evidence of lymphoma
  
  - 10/2013: Initiated on PUVA (psoralen and ultraviolet A radiation) with good response after 9 months of therapy
  - 2014-2016: Lost to follow up
Case 1: Patient IM

• HPI:
  – 2/6/16: admitted to inpatient oncology service with progressive, malodorous, fungating skin lesions, severe pruritis, 10 lb weight loss.
  – PMH: HTN, hyperlipidemia
  – Meds:
    • Atarax
    • Losartan-HCTZ
    • Simvastatin
  – FH: No family history of malignancy
  – SH:
    • Originally from Italy, immigrated 30 years ago
    • Previously worked as a chef
    • Smoking: 0.5 ppd smoker
    • EtOH: occasional

• PE:
  – Vitals: Temp 36.6 BP 114/63 HR 87 SpO2 96% RA
  – Notable for extensive palpable lymphadenopathy
  – Overall, background of fine scaly erythematous coalescent plaques involving face, neck, trunk, genitalia, arms and legs > 90% BSA.
  – Face with hyperkeratotic 1-3 cm papulonodules with nearby eroded plaques.
  – Large plaques on trunk and groin
### Case 1: Patient IM

**Labs:**

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<tr>
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<td>42.5</td>
<td>358</td>
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**Imaging:**

- CT C/A/P: enlarged cervical, supraclavicular, axillary, inguinal LN

**Pathology:**

- Blood: Flow cytometry with atypical T-cell population (CD4+/CD26-) consisting of 2% of lymphocytes.
- FNA of LN **positive** for mycosis fungoides (An atypical T-cell population was identified that was CD4-positive and CD26-negative, accounting for 33% of lymphocytes)
Case 1: Patient IM

Hospital Course:
- Treated with broad spectrum Abx for bacterial superinfection of wounds
- Initiated on systemic therapy through clinical trial of romidepsin and doxorubicin

Case 1: Discussion

• Mycosis Fungoides: Background Information
• Staging Considerations
• Treatment Options
Background: Mycosis Fungoides

- Extramodal indolent non-Hodgkin’s lymphoma of T cell origin with skin manifestations
- Suspect MF in patients who present with chronic nonspecific dermatitis, poikilodermatous skin findings, or generalized erythroderma.
- Skin biopsy is the most critical step in establishing diagnosis
- Represents 4 percent of all cases of non-Hodgkin lymphoma (6 cases per million per year) but is most common type of cutaneous T cell lymphoma.
- Peak age 55-60 years. M > F

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<table>
<thead>
<tr>
<th>Disease of early Mycosis Fungoides</th>
<th>Scoring system</th>
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<tbody>
<tr>
<td>Criteria</td>
<td>Scoring system</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Clinical</td>
<td>2 points for basic criteria and two additional criteria</td>
</tr>
<tr>
<td>Persistent and progressive patchy plaques</td>
<td>1 point for basic criteria and one additional criterion</td>
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<tr>
<td>Additional</td>
<td>1. Not sun-exposed location</td>
</tr>
<tr>
<td></td>
<td>2. Satellite lesions</td>
</tr>
<tr>
<td></td>
<td>3. Nodiokemia</td>
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<tr>
<td>Histopathologic</td>
<td>2 points for basic criteria and two additional criteria</td>
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<tr>
<td>Specific lymphoid infiltrates</td>
<td>1 point for basic criteria and one additional criterion</td>
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<tr>
<td>Additional</td>
<td>1. Dermal proliferation</td>
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<tr>
<td></td>
<td>2. Lymphoid atypia</td>
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<tr>
<td>Molecular biological</td>
<td>1 point for clinical</td>
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<tr>
<td>1. Dermal T-cell receptor gene rearrangement</td>
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<td>Immunopathologic</td>
<td>1 point for any one criteria</td>
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<tr>
<td>1. ≥50 percent CD3+, CD3+, and/or CD5+ T-cells</td>
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<tr>
<td>2. ≥15 percent CD5+ T-cells</td>
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<tr>
<td>3. Dermal/epidermal dissociation of CD4, CD8, or CD56</td>
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* A total of 4 points is required for the diagnosis of mycosis fungoides based on any combination of points from the clinical, histopathologic, molecular biological, and immunopathologic criteria. UptoDate
Mycosis Fungoides: Staging

**Clinical Staging of MF and SS**

<table>
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<th>T</th>
<th>N</th>
<th>M</th>
<th>D</th>
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<td>0-2</td>
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<td>0-2</td>
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<td>0-2</td>
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**Sezary cells in mycosis fungoides**

Reference: Bruning et al.

Mycosis Fungoides: Treatment

**NCCN Guidelines Version 3.2016**

**Suggested Treatment Regimen**

**Systemic Therapies (Continued)**

**Combination Therapies**

Note: All recommendations are ongoing & require further evaluation.
Case 1: Patient IM Update

- Currently completing cycle 3 of romidepsin/doxorubicin with improvement in skin lesions
- Treatment course complicated by challenges of wound care, continued superinfection of wounds
- Possible DRESS syndrome due to romidepsin vs antibiotics
Case 2: Patient JJ

• ID: 32 yo M presenting for with concern for relapsed Hodgkins Lymphoma

• HPI:
  – 1/2015: noted pain less R neck swelling and mass at suprasternal notch
  – 3/21/15: CT chest with multiple enlarged LN
  – 3/26/15 Excisional biopsy of LN: Numerous Reed-Sternberg and Reed-Sternberg variant cells w/ eosinophils and lymphocytes with IHC showing the Reed Sternberg cells to be negative for CD45 and CD20, positive for CD30. Negative for EMA and CD3. Areas of necrosis within the lymph node => Hodgkin Lymphoma, classic type, mixed cellularity variant.
  – 4/12/15: PET/CT with extensive hypermetabolic LN above the diaphragm with no abdominal disease (stage IIA)
  – 5/13/15 C1D1 of ABVD (Doxorubicin 25 mg/m2, Bleomycin 10 units/m2, Vinblastine 6 mg/m2, Dacarbazine 375 mg/m2 on D1 and D15 of 28 day cycles) with plan to follow with radiation
  – 6/20/15 PET/CT (post cycle 2): Resolution of the previously seen metabolically active lymphadenopathy c/w complete response
  – 7/6/15 = C3D1
  – 8/3/15 = C4D1
  – 9/1/15 = C5D1 * Tolerating chemo well, extended to 6 cycles total
  – 9/29/15 = C6D1
  – 12/9/15: Presented with constant frontal/ocular HA, photophobia, and fevers/chills. WBC 18k with negative D workup
  – 12/21/15: Ongoing fevers. CT C/A/P with new 3 cm left hilar lymph node encasing the LLL pulmonary artery, 6 cm lymph node in the subcarinal region, abdomen with 3 new LN in gastrohepatic ligament

Case 2: Patient JJ

• PMH: None
• PSH: Elbow surgery
• Meds: Advil PRN
• Allergies: NKDA
• FH:
  – Paternal grandmother: Brain Tumor
• SH:
  – Married, lives in Hydesville, CA.
  – Smoking: 1 ppd x 15 years, now quit
  – EtOH: occasional
  – Previously worked as a timber feller, not actively
Case 2: Patient JJ

- PE
  - Vitals: Temp 37.0 BP 124/69 HR 99 SpO2 97% on RA
  - General: Young man, well appearing, well developed, in NAD
  - HEENT: Anicteric sclerae, MMMs, no oral lesions
  - Lymph: No palpable cervical, supraclavicular, axillary, or inguinal adenopathy
  - CV: RRR, no murmurs, rubs or gallops
  - Lungs: CTA bilaterally
  - Abdomen: Soft, NT. No palpable hepatosplenomegaly
  - Neuro: No focal neuro deficits

- Labs
  - Cr 0.9
  - LDH 168
  - ANC 12.1
  - ALC 2.83

- Pathology
  - FNA station 7 LN (chest): Recurrent classical Hodgkins Lymphoma
    - Hypercellular aspirate with large atypical cells in background of small lymphocytes and eosinophils
    - Atypical cells with multi-lobated nuclei, prominent nucleoli, large cytoplasm
    - CD 3/15/20 negative, CD30 positive
  - Neck LN excision: confirms Hodgkins
Clinical Question: What therapeutic options are available for his relapse?

Case 2: Patient JJ

- Relapsed Hodgkins Lymphoma
  - Step 1: Confirmation of relapse with imaging and repeat biopsy
    - Path shows diagnostic Reed-Sternberg cells (CD15/30 positive) in an inflammatory background (“starry sky”)
  - Relapse rate: 10-20% in stage I-II disease, 30-40% in advanced disease.
  - Time to relapse: Majority of relapses after complete remission are within 3 years. 40% within first 12 months
- Salvage Options:
  - **High dose chemotherapy and autologous HCT is the standard of care for relapse with non-localized disease**
  - **Note:** Patients with **limited** relapse at > 12 mo after treatment may be treated with chemo +/- radiation
Case 2: Patient JJ

- Lancet 2002
- Relapsed HL comparison of autologous HCT versus conventional chemotherapy.
- Autologous HCT 3 year freedom from treatment failure 55% v 34% for chemo alone
- NO overall survival benefit

![Graph: Freedom from treatment failure for patients with relapsed chemosensitive Hodgkin’s disease]

**Principles of Systemic Therapy for Relapsed or Refractory Disease**

**Regimen:**
- The selection of second-line chemotherapy regimens depends on the pattern of failure and the drugs previously used.
- Patients in complete response to second-line therapy have improved outcomes following HDT/ASCR.
- Brentuximab vedotin is a treatment option if HDT/ASCR has failed or at least 2 prior multi-agent chemotherapy regimens have failed.
- In selected patients, brentuximab vedotin can be used as second-line therapy prior to HDT/ASCR to minimize the use of more intensive regimens.

**Second-Line or Subsequent Therapy Options (listed in alphabetical order):**
- Brentuximab vedotin (only for CHL)
- C-MOPP (cyclophosphamide, vincristine, procarbazine, prednisone) (category 2R)
- EPOCH (etoposide, vincristine, prednisone, cyclophosphamide, doxorubicin)
- ESHAP (etoposide, methylprednisolone, high-dose cytarabine and cisplatin)7,8
- GCD (gemcitabine, carboplatin, dacarbazine)9
- GVD (gemcitabine, vinorelbine, liposomal doxorubicin)9
- ICE (ifosfamide, carboplatin, etoposide)10,11
- MACE (mesna, carboplatin, etoposide, cytarabine)12
- BEAC (cisplatin, etoposide, cytarabine, topotecan)13
- MACE (mesna, etoposide, cytarabine, topotecan)13
- MACE-EMA (etoposide, methotrexate, cytarabine, amifostine)14
- MACE-M (mesna, etoposide, cytarabine, topotecan, mesna, mitoxantrone)15
- MACE-M (mesna, etoposide, cytarabine, topotecan, mesna, melphalan)16

**Additional Therapy Options** (only for CHL) (listed in alphabetical order):
- Bexarotene17
- Cisplatin18
- Doxorubicin18
- Etoposide18
- Nivolumab19,20
- Pantostatin21

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**Post transplant consolidation: Brentuximab**
- Brentuximab is an antibody-drug conjugate targeting CD30

- AETHERA trial: 329 patients assigned to brentuximab versus placebo as maintenance after autologous HCT
- Median PFS for brentuximab was 42.9 months vs 24.1 months for placebo
- Adverse events: peripheral sensory neuropathy and neutropenia
Case 2: Patient JJ Update

- Therapeutic Plan
  - Attempt salvage with ifosfamide, carboplatin, etoposide (ICE) regimen followed by autologous HCT with plan for brentuximab consolidation after therapy
- 2/3/16 C1D1 ICE
- 2/25/16 C2D1 ICE
- 3/9/16: PET/CT with interval decrease in size and hypermetabolism of mediastinal, hilar and gastrohepatic ligament lymphadenopathy, consistent with Deauville 2.
- 3/17/16: Admitted for Cycle 3 ICE + stem cell collection
- Before auto HCT could be completed, patient had fevers, sweating and c/o chest fullness. Pulmonary nodules noted on CT with no change on voriconazole. Bronchoscopy unrevealing.
- 4/14/15 PET CT: Interval development of extensive new hypermetabolic lymphadenopathy in the neck, chest, abdomen and pelvis. Deauville score: 5-2. Continued interval increase in the size of pulmonary nodules in comparison with the very recent CT chest of 4/5/2015. Findings may reflect worsening of infection or lymphoma
- Now initiated on salvage with combination of bendamustine + brentuximab

Case 2: Patient JJ

- Future Directions
  - Nivolumab in Relapsed/Refractory HL (NEJM Jan 2015):
    - 23 heavily pretreated HL patients received nivolumab (anti PD1 Ab), 3 mg/kg q2 weeks
    - ORR 87% (70% with PR, 17% with CR)
    - No Grade 4/5 adverse events
Case 3: Patient SC

ID: 67 yo F with referred for evaluation of autologous transplant for myeloma

HPI: 7/2008: Diagnosed IgA lambda Myeloma.
- Initial Labs: Hgb 9.8 Cr 0.7, Ca 9.4, LDH 300
- Bone marrow biopsy with 95% Plasma cells.
- FISH t(11;14)
- R-ISS Stage III (beta 2 microglobulin > 5.5, elevated LDH)

PMH: No significant PMH

MEDS: Velcade, Decadron, Neurontin, Fentanyl, Docusate, Senna

ALLERGIES: No known drug allergies.

SOCIAL HISTORY:
- lives with her husband and has one daughter and one son.
- works as a realtor
- Denies smoking, tobacco use

Case 3: Patient SC

Treatment Summary:

8/2008 to 1/19/2009: Velcade + dexamethasone. Achieved very good partial response (VGPR)
8/18/2009: Progression of disease, treated with Velcade + revlimid + dexamethasone x 4 cycles. Achieved VGPR.
3/12/2010: Referred to UCSF for autologous stem cell transplant with CR.
10/14/2011: M spine 0 to 0.4, IgA from 77 to 541, Lambda LC from < 5.7 to 16. Resumed revlimid
1/18/2013: M spike 2.2, Lambda LC 46. Started Carfilzomib
4/15/2013: M spike 2.8, Started Carfilzomib + weekly dexamethasone + Cytoxan PO
6/28/2013: M spike 0.92, Lambda LC 14.8
9/22/2013: M spike 0.3, Lambda LC 7.78
2/14/2014: M-spike 0.23, Lambda LC 12.6. Dose reduced dexamethasone due to side effects
Case 3: Patient SC

HPI contd:

5/9/2014: M-spike 0.36, dexamethasone increased back to 20 mg Qweek
10/7/2014: M spike 0.9, Lambda LC 33
11/1/2014: Initiated on CLAPD (Clarithromycin + Pomalidomide + Dexamethasone)
1/26/2015: M spike 0.72
7/28/15: M spike 1.95, patient with neutropenia requiring GCSF
8/18/15: M-spike 1.29, lambda 27. Break from chemo
9/29/15: M spike 1.17. IgA 2151, Lambda LC 88.3871
10/7/15: Initiated Daratumumab. Initial infusion with flushing, mild chest tightness
11/2/15: IgA 1182.
11/30/15: M spike 0.6, Lambda LC 5.8, IgA 181
4/26/16: M spike 0.09, Lambda LC 6.89, IgA 107 (VGPR). Completed 18 doses of daratumumab, did require GCSF in earlier cycles

Case 3: Patient SC

- Therapeutic Summary
  - Velcade + Dexamethasone
  - Velcade + Dexamethasone + Revlimid
  - Autologous Stem Cell Transplant
  - Revlimid
  - Velcade + Dexamethasone
  - Carfilzombib
  - Carfilzombib + Dexamethasone + Cyclophosphamide
  - Clarithromycin + Pomalidomide + Dexamethasone
  - High dose Cyclophosphamide
  - Daratumumab
Case 3: Discussion

• Review MM Diagnostic Criteria
• Risk adjusted treatment strategies
• Role of Autologous HCT
• Treatment Considerations for Daratumumab

Case 3: Discussion

• 2014 International Myeloma Working Group Definition
  – Both Criteria Must be Met:
    1) Clonal bone marrow plasma cells > 10% or biopsy proven bony or extramedullary plasmacytoma
    2) 1 or more of myeloma defining effects (CRAB criteria)
      • Evidence of end-organ damage that can be attributed to plasma cell proliferative disorder
        – Hypercalcemia
        – Renal insufficiency
        – Anemia
        – Bone lesions
        – Clonal bone marrow plasma cells > 60%
        – Involved:uninvolved serum FLC ratio > 100
        – > 1 focal lesion on MRI that is at least 5 mm
Case 3: Discussion

Staging

Revised International Staging System (R-ISS) for MM

- **R-ISS I** (n = 87):
  - Including ISS stage I (serum β₂-microglobulin level < 3.5 mg/L and serum albumin level > 3.5 g/dL)
  - No high-risk CA (kappa (k) or lambda (λ)) and/or t(14;16) and/or t(14;16)
  - Normal LDH level (less than the upper limit of normal range)
- **R-ISS II** (n = 296):
  - Including ISS stage II (serum β₂-microglobulin level > 5.5 mg/L)
  - High-risk CA or high LDH level
- **R-ISS III** (n = 1,804):
  - Including all the other possible combinations

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<th>5-Year OS*</th>
<th>5-Year PFS*</th>
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<tr>
<td>R-ISS I</td>
<td>82%</td>
<td>55%</td>
</tr>
<tr>
<td>R-ISS II</td>
<td>62%</td>
<td>36%</td>
</tr>
<tr>
<td>R-ISS III</td>
<td>40%</td>
<td>24%</td>
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*At a median follow-up of 46 months

Risk Stratification

- **High Risk:**
  - 17p deletion
  - t(14;16)
  - t(14;20)
  - High risk gene expression signature
- **Intermediate Risk:**
  - t(4;14)
- **Standard Risk:**
  - Trisomies
  - t(11;14)
  - t(6;14)

- www.mSMART.org

Case 3: Discussion

**Initial treatment of multiple myeloma by risk stratification**

- **High risk**
  - Patients with t(14;16), t(14;20), and/or t(14;16) have poor outcomes
  - With high risk gene expression profiling signature
  - 4 cycles of VD (prednisolone, doxorubicin, dexamethasone) (if VDH or HDT)

- **Intermediate risk**
  - Patients with t(14;16) only
  - No high-risk CA
  - 4 cycles of VDH or t(14;16) detectable by conventional cytogenetics
  - Autologous HDT if eligible

- **Standard risk**
  - All patients with multiple myeloma who lack any of the high or intermediate risk genetic abnormalities
  - 4 cycles of VDH
  - Eligible for transplant?
    - Yes
    - No
  - Autologous HDT
  - Autologous HDT if eligible
  - Pembrolizumab, maintenance if not in CR

- Autologous Stem Cell Transplantation (ASCT) has shown improvement in overall survival compared with nontransplant cohorts
- Stem cell transplantation is capable of achieving residual disease negativity a predictor of progression free survival
- Ongoing studies to evaluate for early vs late transplant in era of novel drugs/combinations
- In standard risk patients responding well to therapy, ASCT can be delayed until first relapse provided early stem cell harvest
Case 3 Discussion

WHEN TO ADJUST THERAPY?

- PD, progressive disease
- Increase of ≥23% from lowest response value in any of the following:
  - Serum M component with absolute increase ≥6.5 g/dL; serum M component increases ≥21 g/dL are sufficient to define relapse if starting M component is ≥25 g/dL and/or;
  - Urine M component (absolute increase must be ≥100 mg/24 h) and/or;
  - Only in patients without measurable serum and urine M-protein levels: decrease between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL);
  - Only in patients with measurable serum and urine M-protein levels and without measurable disease by FLC level, bone marrow plasma cell percentage (absolute percentage must be ≥10%);
  - Development of new or definite increase in size of existing bone lesions or soft tissue plasmacytoma;
  - Development of hypercalcemia that can be attributed solely to plasma cell proliferative disorder

Two consecutive assessments before new treatment are needed.
Case 3: Discussion

- Daratumumab
  - False positive indirect antiglobulin test
  - Frequent infusion related events (40-70%)
    - Premedicate with methylprednisolone, tylenol, antihistamine
    - Oral steroids on day 1,2 after infusion can prevent delayed reaction
    - Do not administer to moderate/severe persistent asthma or COPD with FEV1 < 50%
  - Cytopenias
    - Grade 3/4 lymphocytopenia: 40%
    - Grade 3/4 neutropenia: 20%
    - Grade 3/4 anemia/thrombocytopenia: 18%

References

- Lokhorst et al. NEJM 373:1207-1219 [September 24, 2015]
- Palumbo et al JCO 2015; 33(28), 2863-2869
- Rajkumar V. Am J Hematology Volume 89, Issue 10, October 2014, 998-1009
- NCCN guidelines
- UptoDate
Questions?

THANK YOU