Inpatient Cancer Care
ACP Puerto Rico Chapter Annual Meeting

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Question 1

A 55 year old gentleman was treated nine days ago with chimeric antigen receptor T cell therapy (CAR-T) for relapsed diffuse large B cell lymphoma. He presents to the clinic with fever, chills, and lightheadedness. He is having difficulty describing his symptoms, but he is clearly unwell.

Vitals: BP 85/60, HR 120, O2 sat 94%, Temp 39.0 C

Exam: unremarkable

Neuro assessment: word finding difficulty, altered handwriting

Labs:
Hg 11.0
WBC 1.0, 980 neutrophils
Plt 40,000

Ferritin: 1,235
CRP: 257
Cr: 1.2
LFT: normal
Question 1

• What is the likely cause of his presentation?
• A. Neutropenic fever with sepsis
• B. CNS relapse of disease
• C. Cytokine release syndrome
• D. Neurotoxicity from CAR-T
• E. C and D
• F. All of the above
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<table>
<thead>
<tr>
<th>Domain</th>
<th>Neelapu et al</th>
<th>Schuster et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CD19 antibody variable domains</td>
<td>FMC63</td>
<td>FMC63</td>
</tr>
<tr>
<td>Transmembrane domain</td>
<td>CD28</td>
<td>CD8</td>
</tr>
<tr>
<td>Costimulatory domain</td>
<td>CD28</td>
<td>4-1BB</td>
</tr>
<tr>
<td>TCR signaling domain</td>
<td>CD3-ζ</td>
<td>CD3-ζ</td>
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</tbody>
</table>

Tran et al, NEJM 377;26
Tran et al, NEJM 377:26
# Efficacy of CAR-T Therapy

<table>
<thead>
<tr>
<th>Disease</th>
<th>Response Rates (%)</th>
<th>Notes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult B-Cell ALL*</td>
<td>83-93</td>
<td>High initial remission rates - ? Role of allogeneic SCT</td>
<td>Park et al., Davila et al., Turtle et al.</td>
</tr>
<tr>
<td>Pediatric B-Cell ALL*</td>
<td>68-90</td>
<td>About 25% of patients relapse with a CD19-leukemia, CD22 CAR-T may improve survival</td>
<td>Maude et al., Fry et al., Lee et al.</td>
</tr>
<tr>
<td>Diffuse Large B-Cell Lymphoma</td>
<td>64-86</td>
<td>40-50% of patients have a durable complete response</td>
<td>Turtle et al., Neelapu et al., Schuster et al.</td>
</tr>
<tr>
<td>Follicular Lymphoma</td>
<td>71</td>
<td>Of those that responded, 89% response maintained at median 28.6 month follow up</td>
<td>Schuster et al.</td>
</tr>
</tbody>
</table>

* Acute Lymphoblastic Leukemia
Toxicities from CAR-T Therapy

- Cytokine release syndrome
  - Typically occurs between day 3-5 after infusion of product
  - Second wave may occur day 9-14 after infusion
  - Characterized by hypotension, tachycardia, and hypoxia
  - Treated with tociluzimab
    - IL-6 receptor inhibitor
    - CRS resolves in hours
Toxicities from CAR-T Therapy

• Neurotoxicity
  • Occurs in same timeframe as CRS
  • Etiology is not well understood
  • Characterized by headache, wordfinding difficulties, tremor, somnolence
  • May worsen to cerebral edema
  • Treated with dexamethasone and antiseizure prophylaxis
    • Takes longer to resolve than CRS
Question 2

65 year old man admitted to the hospital with chest pain. Troponins were positive, and the patient underwent coronary angiography. Angiography was negative for stenosis.

ROS +ve for 25lb weight loss, occasional night sweats.

Exam: small, mobile rubbery lymphadenopathy in inguinal area bilaterally, 1-2cm in size

Labs:
- Hg: 9.7
- MCV: 84.7
- WBC: 7.0
- PLT: 455K
- Smear: rouleaux +
- ESR 137
- Iron and TIBC slightly low
- Cr: 1.0
- SPEP: 2.3g/dL M spike in gamma region
- Imm. Fix: monoclonal IgMκ, small IgMκ
- IgG: 822 mg/dL
- IgM: 3250 mg/dL
- IgA: 52 mg/dL
Question 2

The patients’ presentation is most consistent with which of the following diagnoses?

A. Waldenstrom Macroglobulinemia
B. Smoldering Waldenstrom Macroglobulinemia
C. Lymphoplasmacytic lymphoma
D. IgM MGUS
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# The Spectrum of Disease

<table>
<thead>
<tr>
<th></th>
<th>M Spike</th>
<th>BM involvement</th>
<th>Sign/symptom of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM MGUS</td>
<td>&lt;3g/dL</td>
<td>&lt;10%</td>
<td>-</td>
</tr>
<tr>
<td>Smoldering Waldenstrom</td>
<td>&gt;3g/dL</td>
<td>&gt;10%</td>
<td>-</td>
</tr>
<tr>
<td>Waldenstrom macroglobulinemia</td>
<td>Any</td>
<td>&gt;10%</td>
<td>+*</td>
</tr>
<tr>
<td>Lymphoplasmacytic lymphoma</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
</tr>
</tbody>
</table>

*Fatigue, B symptoms, hyper-viscosity, neuropathy, lymphadenopathy, cytopenia
Waldenstrom Macroglobulinemia

- Lymphoplasmacytic lymphoma
  - Neoplasm of small b lymphocytes, plasmacytoid lymphocytes, and plasma cells

- Lymphoplasmacytic lymphoma with:
  - Bone marrow involvement
  - IgM monoclonal gammopathy
    - → Waldenstrom Macroglobulinemia
Waldenstrom Macroglobulinemia

Presentation:

<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>Present at Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fundoscopic abnormalities</td>
<td>34%</td>
</tr>
<tr>
<td>Hyper-viscosity</td>
<td>31%</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>25%</td>
</tr>
<tr>
<td>B symptoms</td>
<td>23%</td>
</tr>
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Question 3

The patient is started on rituximab based therapy. On routine follow-up for the next cycle, he is admitted for excessive fatigue. He states that for the past week, the fatigue has been so bad, he has been limiting his activity, not leaving the house. He also is embarrassed to admit that he has fallen a couple of times in the past two days. He admits his vision has been a little blurry, but he’s needed new glasses for a while, and his allergies have been particularly troublesome lately. Otherwise, he would like to receive his next cycle of treatment.

What is the next step in management?

A. Evaluation for neuropathy

B. Plasmapheresis

C. Placement in SNF

D. Continue chemotherapy
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B. **Plasmapheresis**

C. Placement in SNF

D. Continue chemotherapy
IgM Flare and Hyperviscosity

- Flare
  - Rise of serum IgM ≥25% rise from baseline
  - Occurs most commonly associated with rituximab
  - May take up to 4 months to resolve
  - May precipitate hyper-viscosity syndrome
Hyper-viscosity Syndrome

- Can measure serum viscosity
  - Not precise, but clear correlation:

<table>
<thead>
<tr>
<th>Serum Viscosity</th>
<th>Patients with hyper-viscosity symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 CP</td>
<td>0%</td>
</tr>
<tr>
<td>&gt;4 CP</td>
<td>67%</td>
</tr>
<tr>
<td>&gt;5 CP</td>
<td>75%</td>
</tr>
</tbody>
</table>
Waldenstrom Macroglobulinemia

Treatment:

Asymptomatic → observe/follow*

Symptomatic → require treatment
  • Rituximab based therapy
Question 4

A 65-year-old man was in his usual state of health until he began experiencing fatigue and shortness of breath.

Laboratory investigations reveal:

- Hg: 6 g/dL
- WBC: 40 X10⁹/L
  - 60% blasts
- Plt: 52,000
- Fibrinogen: 205
- INR: 1.1
Question 4

He is admitted to the hospital and appropriate therapy has begun. Peripheral blood flow cytometry shows blasts that are CD19+ and CD20+ (amongst others). What type of leukemia is this phenotype most associated with?

- A. Acute Promyelocytic Leukemia (APL)
- B. FLT3+ Acute myelogenous leukemia (AML)
- C. Acute B Lymphoblastic Leukemia (ALL)
- D. Chronic Lymphocytic Leukemia (CLL)
- E. Mantle Cell Lymphoma (MCL)
- F. None of the above
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Multipotent hematopoietic stem cell (Hemocytoblast)

- Common myeloid progenitor
  - Erythrocyte
  - Mast cell
  - Myeloblast
    - Basophil
    - Neutrophil
    - Eosinophil
    - Monocyte
      - Plasma cell
      - Macrophage

- Common lymphoid progenitor
  - Small lymphocyte
  - Natural killer cell (Large granular lymphocyte)
    - B lymphocyte
    - T lymphocyte
Question 4

- Lab calls to update testing results. His total WBC count is **actually 240k**.
- Over the past 12 hours, profoundly fatigued, develops headache, and dyspnea.
- Evaluation reveals:
  - O2 sat: 88%
  - K+: 5.9
  - Uric acid: 8.3
  - PO4: 6.0
  - Cr: 1.4
  - INR: 1.3
Question 4
Her presentation is most consistent with:

• A. Spontaneous tumor lysis
• B. Blast crisis
• C. DIC
• D. Differentiation syndrome
• E. Neutropenic Fever
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Blast Crisis
- Cell size generally decreases
- Nuclear volume generally decreases
- Nuclear maturation goes from round, fine chromatin to segmented, dark chromatin
- Nuclear-to-cytoplasmic ratio decreases
- No cytoplasmic granules to primary (azurophilic) granules to specific (secondary) granules
Blast Crisis

• Pseudo hypoxemia
• Pseudo hyperkalemia
• Blood transfusion may be hazardous because of increasing the blood viscosity
• Hydroxyurea
• Monitor for tumor lysis and DIC
### Blast Crisis

<table>
<thead>
<tr>
<th>Leukemias (Lymphomas)</th>
<th>Symptomatic</th>
<th>Asymptomatic</th>
</tr>
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<tbody>
<tr>
<td>Acute myeloid leukemia (AML)</td>
<td>( &gt;50,000 )</td>
<td>( &gt;100,000 )</td>
</tr>
<tr>
<td>Acute lymphoid leukemia (ALL)</td>
<td>( &gt;150,000 )</td>
<td>( &gt;300,000 )</td>
</tr>
<tr>
<td>Chronic myeloid leukemia (CML)</td>
<td>( &gt;150,000 )</td>
<td>No</td>
</tr>
<tr>
<td>Chronic lymphoid leukemia (CLL)</td>
<td>( &gt;500,000 )</td>
<td>No</td>
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<td>No</td>
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Question 5

A 65 year old gentleman is diagnosed with chronic lymphocytic leukemia (CLL) and is initiated on ibrutinib. Two months after initiation of therapy, he sees you for routine follow up. Unfortunately, his lymphocyte count has increased from 25,000 to 35,000. He feels fatigued and has intermittent body aches.

What is the next step in management?

A. Stop ibrutinib due to progressive disease
B. PET scan to evaluate for Richter’s transformation
C. Continue ibrutinib despite symptoms
D. Peripheral blood flow cytometry to evaluate for ibrutinib escape
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Ibrutinib side effects/toxicities

- Diarrhea
- Fatigue
- Body aches
- *Elevation* in lymphocyte count
Question 6

This same gentleman was admitted to the hospital after a fall and traumatic fracture to his left hip. He is scheduled for hip surgery later today. He has been on ibrutinib for the past 6 months, and his disease is well controlled.

What would be the optimal management of his ibrutinib?

A. Continue and proceed with surgery
B. Hold ibrutinib for 24 hours then proceed with surgery
C. Hold ibrutinib and delay surgery for 4-7 days
D. Switch ibrutinib to another bruton tyrosine kinase (BTK) inhibitor.
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Ibrutinib and bleeding

- Half of patients will develop low grade ecchymoses and petechiae
  - Defect in platelet aggregation
- Major hemorrhage rates range from 1%-9%
  - May be spontaneous or periprocedural

- Therefore, elective surgeries should be performed before initiation
  - Emergency surgeries case by case
Review

• CART toxicities
• Hyperviscosity syndrome
• Blast crisis
• CLL and Ibrutinib
Thank You

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