Immunotherapy-Related Cytopenias

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Objectives

- Incidence and common presentations of immunotherapy-related cytopenias

- Workup/diagnosis of immunotherapy-related thrombocytopenia, anemia, and neutropenia
  - Immune Thrombocytopenia (ITP)
  - Autoimmune Hemolytic Anemia (AIHA)
  - Autoimmune Neutropenia

- Management of immunotherapy-related cytopenias

- Clinical cases

- Q&A, please share your experiences!
Incidence of Immunotherapy-Related Cytopenias
What about checkpoint inhibitor-related cytopenias?
## Incidence of Checkpoint Inhibitor-Related Cytopenias

<table>
<thead>
<tr>
<th>Cytopenia</th>
<th>Pembrolizumab</th>
<th>Nivolumab</th>
<th>Ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Grade 3-4 (PLT &lt; 50/μL)</td>
<td>12 – 34%</td>
<td>&lt; 1%</td>
<td>3%</td>
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<tr>
<td></td>
<td>4 – 10%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Anemia</strong></td>
<td></td>
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<tr>
<td>Grade 3-4 (Hgb &lt; 8.0 g/dL, req PRBCs)</td>
<td>17 – 54%</td>
<td>26 – 41%</td>
<td>41%</td>
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<tr>
<td></td>
<td>0.5 – 24%</td>
<td>≤ 3%</td>
<td>6%</td>
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<tr>
<td><strong>Neutropenia</strong></td>
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</tr>
<tr>
<td>Grade 3-4 (ANC &lt; 1000/mm3)</td>
<td>7 – 30%</td>
<td>11 – 24%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td></td>
<td>1 – 11%</td>
<td>≤ 2%</td>
<td>NR</td>
</tr>
<tr>
<td>ITP, AIHA, or Autoimmune Neutropenia</td>
<td>≤ 1% overall</td>
<td></td>
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<tr>
<td></td>
<td>Significantly greater percentage of G3-4 heme toxicities</td>
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</tbody>
</table>

NR = Not Reported; Hgb = Hemoglobin; ANC = absolute neutrophil count; ITP = Immune Thrombocytopenia, AIHA = Autoimmune Hemolytic Anemia

Brahmer et al., JCO, 2017
Why do these immunotherapy-related cytopenias happen?
Incidence of Cytopenias

- Observational study from 3 French registries/databases of checkpoint-inhibitor (CPI) toxicities (Delanoy et al., Lancet Haematol., 2018)

- 35 of 948 patients with hematologic immunotherapy-related adverse events (irAEs) autoimmune in nature

- Tumor types: Melanoma (43%), NSCLC (34%), Lymphoma (11%)

- Immunotherapy: Nivolumab (57%), Pembrolizumab (40%), Atezolizumab (3%)
<table>
<thead>
<tr>
<th></th>
<th>All patients (n=35)</th>
<th>Neutropenia (n=9)</th>
<th>Autoimmune haemolytic anaemia (n=9)</th>
<th>Immune thrombocytopenia (n=9)</th>
<th>Pan cytopenia or aplastic anaemia (n=5)</th>
<th>Other* (n=3)</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Median</td>
<td>65 (51-75)</td>
<td>70 (51-77)</td>
<td>64 (51-75)</td>
<td>66 (52-76)</td>
<td>62 (52-74)</td>
<td>69 (53-77)</td>
<td>--</td>
</tr>
<tr>
<td>Range</td>
<td>30-90</td>
<td>34-90</td>
<td>30-89</td>
<td>35-81</td>
<td>54-78</td>
<td>49-82</td>
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</tr>
<tr>
<td>Previously exposed to anti-CTLA4</td>
<td>6 (17%)</td>
<td>0</td>
<td>3 (33%)</td>
<td>2 (22%)</td>
<td>1 (20%)</td>
<td>1 (33%)</td>
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<tr>
<td><strong>Drug class involved</strong></td>
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</tr>
<tr>
<td>Anti-PD-1</td>
<td>34 (97%)</td>
<td>9 (100%)</td>
<td>8 (89%)</td>
<td>9 (100%)</td>
<td>5 (100%)</td>
<td>3 (100%)</td>
<td>--</td>
</tr>
<tr>
<td>Anti-PD-L1</td>
<td>1 (3%)</td>
<td>0</td>
<td>1 (11%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td><strong>Time to onset, weeks</strong></td>
<td>10.1 (3.6-24.1)</td>
<td>10.0 (3.1-19.4)</td>
<td>3.9 (2.5-18.0)</td>
<td>10.1 (4.1-20.5)</td>
<td>21.7 (4.0-25.7)</td>
<td>10.0 (3.4-20.5)</td>
<td>0.427</td>
</tr>
<tr>
<td><strong>Maximum severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Grade 2</td>
<td>3 (9%)</td>
<td>1 (11%)</td>
<td>0</td>
<td>1 (11%)</td>
<td>1 (20%)</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Grade 3</td>
<td>5 (14%)</td>
<td>1 (11%)</td>
<td>1 (11%)</td>
<td>1 (11%)</td>
<td>1 (20%)</td>
<td>1 (33%)</td>
<td>--</td>
</tr>
<tr>
<td>Grade 4</td>
<td>25 (71%)</td>
<td>6 (67%)</td>
<td>8 (89%)</td>
<td>7 (78%)</td>
<td>2 (40%)</td>
<td>2 (67%)</td>
<td>--</td>
</tr>
<tr>
<td>Grade 5</td>
<td>2 (6%)</td>
<td>1 (11%)</td>
<td>0</td>
<td>0</td>
<td>1 (20%)</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td><strong>Duration at grade 2 or worse, weeks</strong></td>
<td>4.2 (1.7-8.9)</td>
<td>2.4 (1.6-10.1)</td>
<td>2.4 (1.7-8.9)</td>
<td>4.4 (1.7-11.3)</td>
<td>6.0 (2.4-12.4)</td>
<td>8.0 (2.7-12.3)</td>
<td>0.422</td>
</tr>
<tr>
<td><strong>Follow-up of haem-irAE, weeks</strong></td>
<td>19.4 (9.4-55.4)</td>
<td>18.4 (9.3-55.3)</td>
<td>9.7 (5.3-25.3)</td>
<td>20.4 (19.9-65.3)</td>
<td>28.7 (8.7-33.1)</td>
<td>46.0 (9.2-60.0)</td>
<td></td>
</tr>
<tr>
<td>Resolution at final follow-up</td>
<td>21 (60%)</td>
<td>6 (67%)</td>
<td>6 (67%)</td>
<td>7 (78%)</td>
<td>1 (20%)</td>
<td>1 (33%)</td>
<td>0.136</td>
</tr>
<tr>
<td>Rechallenge</td>
<td>7 (20%)</td>
<td>3 (33%)</td>
<td>1 (11%)</td>
<td>3 (33%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence of same haem-irAE after rechallenge</td>
<td>3/7 (43%)</td>
<td>2/3 (67%)</td>
<td>0</td>
<td>1/3 (33%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are n (%) or median (IQR) unless otherwise stated. CTLA4=cytotoxic T-lymphocyte protein 4. Haem-irAE=haematological immune-related adverse event. PD-1=programmed cell death 1. PD-L1=programmed cell death ligand 1. *Two patients with bicytopenia and one with pure red cell aplasia. †Significance threshold of p<0.05.

Table 3: Characteristics of haem-irAEs by type

Delanoy et al., Lancet Haematol., 2018
# Autoimmune cytopenias after CPIs

Fattizzo et al., Pharmaceuticals, 2022

<table>
<thead>
<tr>
<th>References</th>
<th>Type of Study</th>
<th>Patients</th>
<th>Frequency</th>
<th>Main Findings</th>
<th>CPI Interruption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delany N et al. (2019) [17]</td>
<td>Observational study</td>
<td>745</td>
<td>3.7%</td>
<td>The most-frequent hematologic IRAEs after anti-FD-1 or anti-PD-L1 were AIHA, ITP or neutropenia (26%), followed by pancytopenia or aplastic anemia (14%). The median time of onset was 10 weeks; most events were grade 4 and resolved after immunosuppressive therapy.</td>
<td>80% of the cases; 20% rechallenge</td>
</tr>
<tr>
<td>Michot JM et al. (2019) [19]</td>
<td>Review</td>
<td>63</td>
<td>3.6%</td>
<td>An incidence of 0.7% for grades 3 to 4 IRAEs, mostly immune cytopenias (17 to 29%), aplastic anemia (19%) and HLH (11%). The median time of onset was of 10 weeks. Resolution varied from 25% for aplastic anemia to 80% for ITP and AIHA, and 14% died. The risk of recurrence after CPI rechallenge was around 50%.</td>
<td>Not reported</td>
</tr>
<tr>
<td>Davis E. J. et al. (2019) [20]</td>
<td>Observational study</td>
<td>164</td>
<td>1% (among all reported adverse events)</td>
<td>AIHA was the most common, mostly associated with melanoma and lung cancer; 25% had an extra-hematological IRAEs; mortality was 11% but increased to 23% in the case of HLH.</td>
<td>Not reported</td>
</tr>
<tr>
<td>Zaremba A. et al. (2021) [16]</td>
<td>Observational study</td>
<td>6961</td>
<td>0.14%</td>
<td>10 patients experienced grade 4 neutropenia (60% possibly due to melainzol), with median time of onset of 6.4 weeks; 40% required systemic steroids, and neutropenia responded to G-CSF. No recurrance was reported after CPI rechallenge.</td>
<td>70%</td>
</tr>
<tr>
<td>Kramer R et al. (2021) [16]</td>
<td>Observational study</td>
<td>7626</td>
<td>0.6%</td>
<td>Mostly autoimmune cytopenias (28–34%), rarely HLH (4%), aplastic anemia (2%), coagulation dysfunction (2%) and acquired hemophilia A (2%). The median time of onset was 25 weeks. 60% required hospitalization, and 80% had complete resolution. AIHA and ITP tended to persist.</td>
<td>60%</td>
</tr>
</tbody>
</table>

Clinical Presentation of Autoimmune Cytopenias
Immune Thrombocytopenia (ITP)

• Common symptoms
  • Often asymptomatic, especially with PLT > 30K/μL
  • Fatigue
  • Petechial rash, purpura
  • Spontaneous bleeding – epistaxis, less commonly severe bleeding
  • Rarely thrombosis

Think of ITP when there is isolated, profound thrombocytopenia with normal Hgb/Hct and WBC/diff
Autoimmune Hemolytic Anemia (AIHA)

• Common symptoms
  • Fatigue
  • Dyspnea on exertion
  • Palpitations, tachycardia
  • Jaundice and/or pallor
  • Dark urine

AIHA can co-occur with ITP = Evans Syndrome
Autoimmune Neutropenia

- Common symptoms
  - Often asymptomatic
  - Can present at the time of an infection

Consider immune neutropenia with new, isolated, profound neutropenia
Workup of Immunotherapy-Related Cytopenias
## Workup of Cytopenias

<table>
<thead>
<tr>
<th>Anemia</th>
<th>Thrombocytopenia</th>
<th>Neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with diff</td>
<td>Immature platelet fraction</td>
<td>Consider other cytopenia tests if concomitant cytopenias</td>
</tr>
<tr>
<td>CMP</td>
<td>PTT/PT/INR, Fibrinogen</td>
<td></td>
</tr>
<tr>
<td>Nutritional studies: Iron/TIBC, Ferritin, B12, Folate</td>
<td>Hemolysis labs if anemia</td>
<td></td>
</tr>
<tr>
<td>Peripheral smear</td>
<td>Reticulocyte count</td>
<td></td>
</tr>
<tr>
<td>LDH, Haptoglobin, Coombs</td>
<td>Immature platelet fraction</td>
<td></td>
</tr>
<tr>
<td>IPF, coags if TCP</td>
<td>PTT/PT/INR, Fibrinogen</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemolysis labs if anemia</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>Consider:</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B/C</td>
<td>ANA, Rheumatoid Factor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EBV, CMV, Parvovirus PCRs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bone marrow biopsy if pancytopenia, risk factors marrow involvement/disorder</td>
<td></td>
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</tbody>
</table>
Management of Immunotherapy-Related Cytopenias
Upfront Treatment of Immunotherapy-Related Cytopenias

• Steroids
  • ITP – Dexamethasone 40mg PO daily x 4 days
  • AIHA – Prednisone 1mg/kg PO daily with gradual taper
  • Neutropenia – will respond to steroids, typically Prednisone 1mg/kg

• IVIG for ITP – 1g/kg daily for 1-2 doses

• GCSF trial for neutropenia
Second-Line Treatment of Immunotherapy-Related Cytopenias

• Rituximab 375mg/m2 IV weekly x 4 weeks
  - Use in standard of care treatment for ITP and AIHA to control disease and prevent relapse (Go et al., Blood, 2017)
  - Can also use in autoimmune neutropenia given overlapping general pathophysiology with autoimmune disorders
  - Data supporting Rituximab use with CPIs without losing therapeutic effects (Damsky et al., 2019)

• Thrombopoietin (TPO) Receptor Agonists for ITP
  - Oral - Eltrombopag, Avatrombopag
  - Romiplostim – SQ TPO peptide mimetic that binds to human TPO receptor
Consider Rechallenge

- If immune-mediated cytopenia in complete response (or good control of chronic ITP), can consider rechallenge with close monitoring.

- Weigh risks/benefits and impact on prognosis with continuing immunotherapy vs changing therapies
  - More important in metastatic disease with limited treatment options
  - More likely discontinue if using in adjuvant setting

- Limited data on recurrence rates of IrAEs with rechallenge
Case 1: Ms. D
Ms. D

- 79yo woman with metastatic NSCLC (glandular squamous/neuroendocrine differentiation) with pleural mets
  - PDL1 50%, negative driver mutations
  - H/o ulcerative colitis s/p colectomy, celiac, DVT/PE on Apixaban
  - Normal CBC at baseline
  - Started Pembrolizumab, completed C1-3 without issue
Ms. D

- Restaging CT TAP day of C4 with significant response in mediastinal/hilar LNs, RLL mass, and pleural mets

- Present to clinic right after scans for clearance prior to C4 Pembro
  - New drop in hemoglobin to 5.9
  - Worsening profound fatigue, exhaustion, chills past 3 weeks
  - Unable able to stand in shower or stir oatmeal 2/2 exhaustion
  - No chest pain, shortness of breath, lightheadedness/dizziness
Ms. D

• Labs on presentation
  • Hgb 5.9, Hct 18.7, **MCV 102.2** PLT 163, WBC 4.21, normal diff
  • Tbili 1.5, normal AST/ALT/Alk Phos, Cr 1.4 (baseline)

• Further workup on admission
  • Tsat 65%, Ferritin 847, B12 1400, Folate 18.0, TSH 1.427, FT4 0.8
  • Elevated immature retic fraction 15.9%, retic 3.73%
  • LDH 518 (normal 135-225)
  • Haptoglobin < 8
  • Coombs positive for IgG, negative for C3

**New diagnosis of AIHA**
Ms. D

• **Treatment course**
  - Transfused PRBCs
  - Started Prednisone 1mg/kg PO daily
  - Received upfront Rituximab 375mg/m² IV weekly x 4 weeks after discharge
  - Was able to finally taper off Prednisone completely 12 weeks after diagnosis of AIHA

• **Observed for her lung cancer while on Prednisone/Rituximab**
  - Restaging scans during final week of Prednisone showed ongoing response with further decrease in disease despite holding Pembrolizumab
  - Patient & thoracic oncologist opted for continued observation as she was asymptomatic

• **Mild progression of disease in mediastinal lymphadenopathy and new hypercalcemia on next CTs 3 months later**
  - Decided to change to Atezolizumab to see if reduced risk of recurrent AIHA (anecdotal)
  - Remains on Atezolizumab, currently 3 cycles in with no hemolysis
Case 2: Mr. J
Mr. J

• 68yo gentleman with history of muscle invasive bladder cancer
  • Received neoadjuvant ddMVAC followed by radical cystoprostatectomy and BPLND with ypT0N1 disease
  • Started adjuvant Nivolumab with plan for 1 year
  • Received 8 cycles of Nivolumab 480mg q4weeks

• Presented for C9 Nivolumab clearance, asymptomatic
Mr. J

• **Pre-treatment labs**
  - WBC 1.96K (from 3.95, baseline 4-8)
  - ANC 0.14 (from 2.07, baseline 2-5K)
  - Normal Hgb 15.2, MCV 84.4, PLT 210K

• Held treatment and referred to Hematology for further workup
  - Normal retic, IPF, B12, Folate, Copper, CMP
  - Negative HIV, Hepatitis B/C, ANA, Rheumatoid Factor
  - Peripheral smear with neutropenia, otherwise unremarkable

• Developed pyelonephritis with E. coli bacteremia 1 week into being newly neutropenic, admitted and treated
Mr. J

- Bone marrow biopsy obtained since he had prior chemo/anthracycline exposure
  - Mild hypocellularity (20%), no significant dysplasia, no increased blasts
  - Small clonal CD8+ T-LGL population and ~3% unevenly distributed mast cell populations – can be seen in the post-chemo setting
  - Normal cytogenetics, MDS FISH
  - NGS with DNMT3a splice variant c.1851+2T>G at low VAF 3%

- Question of Clonal Cytopenia of Undetermined Significance (CCUS) as diagnosis per pathology but otherwise unremarkable bone marrow
  - CCUS would not explain the acute, profound drop in ANC
Mr. J

• **Treatment course**
  - Started Prednisone 1mg/kg with acute response, unable to tolerate 2/2 severe hyperglycemia
  - ANC not responsive to GCSF
  - Started Rituximab 375mg/m² IV weekly x 4 weeks

• **ANC responded quickly after 1 dose of Rituximab, 0.22 >> 4.07 after one week**
  - Subsequently hospitalized for new immunotherapy-related adrenal insufficiency, unable to receive further doses Rituximab
  - Held Rituximab while being stabilized for adrenal insufficiency, started on Hydrocortisone/Fludrocortisone
• ANC held in 2-4K range for 2 months, then acutely dropped again to ANC 0.12, asymptomatic

• Completed Rituximab 375mg/m2 IV weekly x 4 weeks

• ANC again quickly normalized, remains within normal range ~3 months out thus far, remains on observation
Case 3: Mr. L
Mr. L

- 70yo gentleman with history of newly diagnosed metastatic clear cell renal cell carcinoma
  - Prior open right radical nephrectomy 2 years prior, now with recurrent/metastatic disease to lungs
  - History of chronic ITP diagnosed 10 years prior, observed only, never required treatment
  - Baseline PLT 90K-120K over the years
  - Started Pembrolizumab/Axitinib for first-line therapy
Mr. L

• Completed 4 cycles of Pembrolizumab/Axitinib
  • Presented for C5 Pembrolizumab/Axitinib, asymptomatic
  • Pre-treatment labs:
    • PLT 40K (from 160-170K past few months)
    • Normal Hgb 14.4, MCV 86.1, WBC 4.95, normal diff
    • Referred to Heme

• Lab Workup
  • Normal CMP, B12, Folate, coags
  • Negative HIV, Hepatitis B/C
Mr. L

- Since ITP asymptomatic with PLT > 30K, continued observation
  - Weighed risks/benefits of continuing Pembrolizumab and consideration of Rituximab/TPO receptor agonists
  - Pembrolizumab rescheduled, platelets increased to 92K with pre-treatment labs
    - Unfortunately had new G3 immunotherapy-related colitis and inflammatory arthritis on clinical assessment
    - Started Prednisone for colitis/inflammatory arthritis
    - Pembrolizumab discontinued

- Continues on Cabozantinib monotherapy currently
- Chronic ITP remains on observation with PLT at baseline 90-120K
References


Questions or Patient Experiences?