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

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Management of Immunotherapy-Related Toxicities

NCCN Guidelines Index
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Discussion

Immune Checkpoint Inhibitor-Related Toxicities

Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

Lymphocyte Engager-Related Toxicities

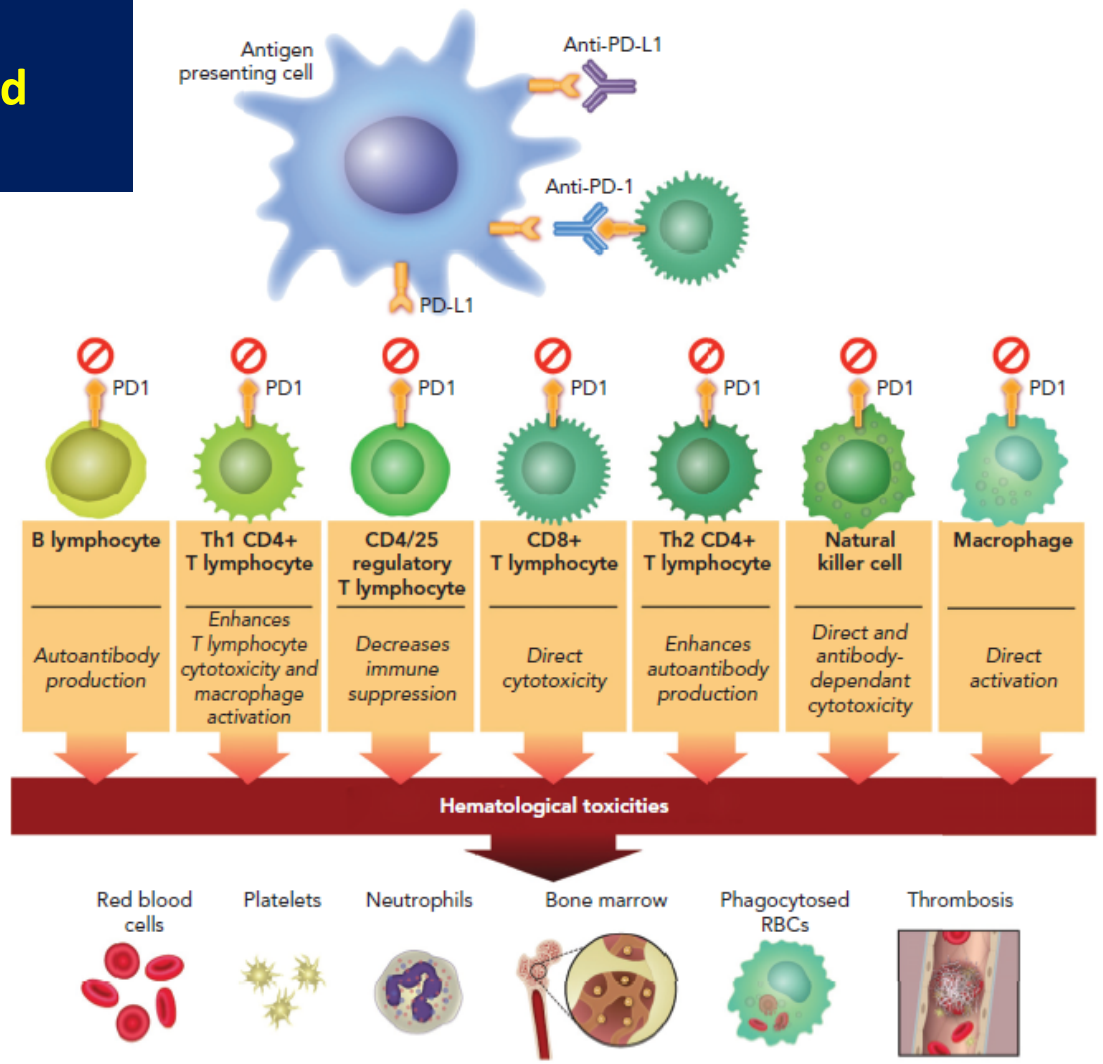
What about checkpoint inhibitor-related cytopenias?

Incidence of Checkpoint Inhibitor-Related Cytopenias

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

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?



Delanoy et al., Lancet Haematol., 2018

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%)

	All patients (n=35)
Type of haem-irAE	
Neutropenia	9 (26%)
Anaemia	9 (26%)
Thrombocytopenia	9 (26%)
Pancytopenia or aplastic anaemia	5 (14%)
Bicytopenia	2 (6%)
Pure red cell aplasia	1 (3%)
Class of anti-PD-1 or PD-L1 immunotherapy given	
Nivolumab	20 (57%)
Pembrolizumab	14 (40%)
Atezolizumab	1 (3%)
Case causality assessment between anti-PD-1 or PD-L1 and haem-irAE*	
Certain	18 (51%)
Probable	17 (49%)
Treatment of haem-IrAEs	
Steroids, oral	22 (63%)
Steroids, intravenous and oral	5 (14%)
Immunoglobulins, intravenous	11 (31%)
Rituximab	7 (20%)
Supportive care	
Transfusion (red blood cells or platelets)	15 (43%)
Granulocyte colony-stimulating factor	12 (34%)
Erythropoiesis-stimulating drug	2 (6%)
Thrombopoietin agonist	3 (9%)
Deaths	
Cancer progression	9 (26%)
Haem-irAE related to anti-PD-1 or PD-L1 treatment	2 (6%)
Concomitant illness†	1 (3%)
Follow-up duration, weeks	19·4 (9·4-55·4)

	All patients (n=35)	Neutropenia (n=9)	Autoimmune haemolytic anaemia (n=9)	Immune thrombocytopenia (n=9)	Pancytopenia or aplastic anaemia (n=5)	Other* (n=3)	p value†
Age, years							
Median	65 (51–75)	70 (51–77)	64 (51–75)	66 (52–76)	62 (52–74)	69 (53–77)	..
Range	30–90	34–90	30–89	35–81	54–78	49–82	..
Previously exposed to anti-CTLA4	6 (17%)	0	3 (33%)	2 (22%)	1 (20%)	1 (33%)	..
Drug class involved							
Anti-PD-1	34 (97%)	9 (100%)	8 (89%)	9 (100%)	5 (100%)	3 (100%)	..
Anti-PD-L1	1 (3%)	0	1 (11%)	0	0	0	..
Time to onset, weeks	10·1 (3·6–24·1)	10·0 (3·1–19·4)	3·9 (2·5–18·0)	10·1 (4·1–20·5)	21·7 (4·0–25·7)	10·0 (3·4–20·5)	0·427
Maximum severity							
Grade 2	3 (9%)	1 (11%)	0	1 (11%)	1 (20%)	0	..
Grade 3	5 (14%)	1 (11%)	1 (11%)	1 (11%)	1 (20%)	1 (33%)	..
Grade 4	25 (71%)	6 (67%)	8 (89%)	7 (78%)	2 (40%)	2 (67%)	..
Grade 5	2 (6%)	1 (11%)	0	0	1 (20%)	0	..
Duration at grade 2 or worse, weeks	4·2 (1·7–8·9)	2·4 (1·6–10·1)	2·4 (1·7–8·9)	4·4 (1·7–11·3)	6·0 (2·4–12·4)	8·0 (2·7–12·3)	0·422
Follow-up of haem-irAE, weeks	19·4 (9·4–55·4)	18·4 (9·3–55·3)	9·7 (5·3–25·3)	20·4 (10·9–65·3)	28·7 (8·7–33·1)	46·0 (9·2–60·0)	..
Resolution at final follow-up	21 (60%)	6 (67%)	6 (67%)	7 (78%)	1 (20%)	1 (33%)	0·136
Rechallenge	7 (20%)	3 (33%)	1 (11%)	3 (33%)	..	..	..
Recurrence of same haem-irAE after rechallenge	3/7 (43%)	2/3 (67%)	0	1/3 (33%)	..	..	..

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 1. Hematological toxicities after checkpoint inhibitors (CPI).

References	Type of Study	Patients	Frequency	Main Findings	CPI Interruption
Delanoy N et al. (2019) [17]	Observational study	745	3.7%	The most-frequent hematologic IRAEs after anti-PD-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.	80% of the cases 20% rechallenge
Michot JM et al. (2019) [19]	Review	63	3.6%	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%.	Not reported
Davis E.J. et al. (2019) [20]	Observational study	164	1% (among all reported adverse events)	AIHA was the most common, mostly associated with melanoma and lung cancer; 23% had an extra-hematological IRAEs; mortality was 11% but increased to 23% in the case of HLH.	Not reported
Zaremba A. et al. (2021) [18]	Observational study	6961	0.14%	10 patients experienced grade 4 neutropenia (60% possibly due to metamizole), with median time of onset of 6.4 weeks; 40% required systemic steroids, and neutropenia responded to G-CSF. No recurrence was reported after CPI rechallenge.	70%
Kramer R et al. (2021) [16]	Observational study	7626	0.6%	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.	60%

IRAEs immune-related adverse events, ITP: immune thrombocytopenia, AIHA: autoimmune hemolytic anemia, HLH: hemophagocytic lymphohistiocytosis, G-CSF: granulocyte colony stimulating factor.

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

Anemia	Thrombocytopenia	Neutropenia
CBC with diff CMP Nutritional studies: Iron/TIBC, Ferritin, B12, Folate Peripheral smear		
Reticulocyte count LDH, Haptoglobin, Coombs IPF, coags if TCP	Immature platelet fraction PTT/PT/INR, Fibrinogen Hemolysis labs if anemia	Consider other cytopenia tests if concomitant cytopenias
	HIV Hepatitis B/C	
Consider: ANA, Rheumatoid Factor EBV, CMV, Parvovirus PCRs Bone marrow biopsy if pancytopenia, risk factors marrow involvement/disorder		

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

- Presented 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

Mr. J

- 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

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Questions or Patient Experiences?