Neurologic Complications and Management in the Era of Checkpoint Inhibitors

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Immune Checkpoints

- Immune checkpoints: the set of inhibitory pathways that immune cells possess in order to regulate and control the durability of the immune response while maintaining self-tolerance.
- Key players in this pathway are PD1/PDL1 and CTLA4
- Tumors, particularly those with high mutation frequency such as melanoma, can co-opt these checkpoints and evade immune detection

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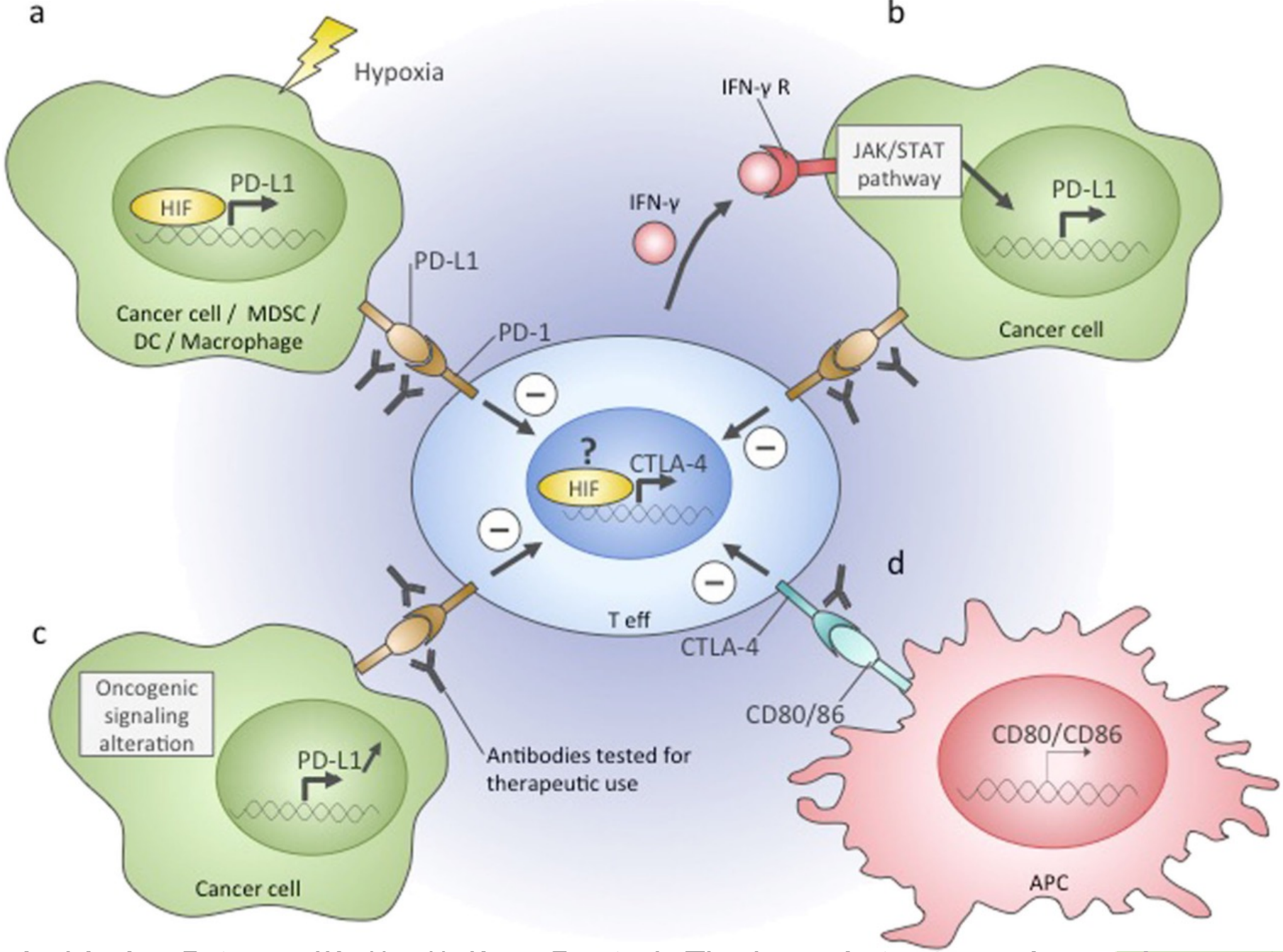

Petrova, V., Annicchiarico-Petruzzelli, M., Melino, G. et al. The hypoxic tumour microenvironment. Oncogenesis 7, 10 (2018).

Immune Checkpoint Inhibitors (CPI)

- Medications that interfere with this pathway
- Antibodies targeting PD1/PDL1 and CTLA4
- Allows immune system to bypass the co-opted checkpoints expressed on tumor cells
- Remove the checkpoints in tumors but also in healthy tissue
- This can lead to failure of tolerance and development of autoimmune disease
- Approved for more than 60 indications

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Medications in this class/targets

- PD1
  - Pembrolizumab
  - Nivolumab
  - Cemipilimab
  - Pidilizumab
- PDL1
  - Atezolizumab
  - Avelumab
  - Durvalumab
- CTLA4
  - Ipilimumab
  - Tremelimumab

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Neurologic Immune-Related Adverse Events (irAE-Ns) associated with CPI

- Incidence ranges from 1-12%
- PNS twice as often affected as the CNS
- Higher risk of fatal outcome (also with myocarditis)

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Guidon AC, Burton LB, Chwalisz BK et al. Consensus disease definitions for neurologic immune-related adverse events of immune checkpoint inhibitors
J Immunother Cancer. 2021 Jul;9(7). PMID: 34281989

Neurologic Immune Related Adverse Events (irAE-Ns) associated with CPI: CNS

- CNS
  - Encephalitis: brain only
  - Encephalomyelitis: brain + spinal cord
  - Meningoencephalitis: meninges and brain
  - Meningitis: meninges only
  - Vasculitis (stroke, hemorrhage, enhancement, HA, sz, rash); isolated or with systemic
- Brain: confusion, seizures, personality change, altered LOC
- Meninges: meningismus, headache, stiff neck, N/V, visual phenomena
- Spinal cord: myelopathy (weakness, sensory disturbance, bowel/bladder dysfunction)
- Must have CSF and contrast MRI (MRI before LP-can cause enhancement)

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Specific CNS CPI related conditions

- Cerebellitis, limbic encephalitis, rhombencephalitis
- Opsoclonus myoclonus ataxia
- Stiff person syndrome/ progressive encephalomyelitis with rigidity and myoclonus (PERM)
- CNS Demyelinating conditions
  - Optic neuritis
  - Acute disseminated encephalomyelitis (ADEM; MRI looks like MS)
  - AHEM
  - RIS
  - Work-up should include aquaporin and MOG antibodies (serum +/- CSF)

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Neurologic Autoimmune Conditions associated with CPI: PNS

- Myopathy/Myositis: weakness (proximal > distal), myalgia, cramps
  - Immune mediated necrotizing myopathy also
  - Myositis often with cranial nerve involvement (ptosis, diplopia, dysphagia, etc)
  - Seen with MG and distinguishing myopathy and MG difficult
- Peripheral nerve (cranial neuropathy +/- polyradiculoneuropathy most common); rarely isolated neuropathy
  - AIDP (and variants), CIDP (and varints), MMN
  - Mononeuritis multiplex: Vasculitis isolated PNS or systemic
  - Brachial neuritis, LS radiculoplexus neuropathy
- Myasthenia gravis: high rate of concurrent myopathy and myocarditis
- Evaluate with EMG/NCS, possible rep stim, CK, antibody testing, MRI

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Criteria for diagnosis of Neurologic irAE's

- Onset < 12 months from last dose of CPI
- Baseline exam for existing autoimmune neurologic disease to establish a change after CPI administration
- Presence of concurrent immune-related AEs (ex myocarditis with myasthenia gravis) increases likelihood of cause and effect
- Improves with stopping CPI or treatment with steroids (lack of improvement does not exclude but warrants further investigation for alternative etiologies)
- Non-specific symptoms (HA, confusion, fatigue, tremor) not sufficient
- Autoantibodies (AChR Ab MG; CRMP5 myelitis; aquaporin-4 NMO) supportive but not mandatory

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Treatment of CPI Related Neurologic Complications

- Stop the CPI
- May observe if mild
- Steroids
  - Prednisone 0.5-1.5 mg/kg daily (high end dose for MG) for mild (Grade 2)
  - IV Methylprednisolone 1-2 mg/kg. Consider 1 g daily for myelopathy (for grade 3 or 4)
- IVIg specifically for grade 3-4 peripheral nerve/nerve root grade 3 or 4 (GBS). Unlike idiopathic steroids can be used for CPI related GBS. Also may be used for grade 3 or 4 myopathy
- Plasma exchange for GBS as alternative to IVIg, steroids. May be used also for grade 3 or 4 myopathy
- MG: pyridostigmine, prednisone; steroids + IVIg or PLEX and ICU for grade 3 or 4

Reynolds KL and Guidon AC. Diagnosis and Management of Immune Checkpoint Inhibitor-Associated Neurologic Toxicity: Illustrative Case and Review of the Literature. Oncologist. 2019 Apr; 24(4): 435–443. PMID: 30482825

Conclusions

- Neurologic adverse events related to check point inhibitor treatment are not rare and need to be recognized and treated
- CNS and PNS are both affected but PNS more common
- These neurologic complications usually respond to immunosuppression or immunomodulation but can have permanent residual deficits
- Steroids are first-line therapy

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