PRACTICE AID

Guide to Managing Adverse Events Associated With Immune Checkpoint Inhibitors and TKIs[1,2]

PeerView Oncology

MLI Medical Learning Institute, Inc.

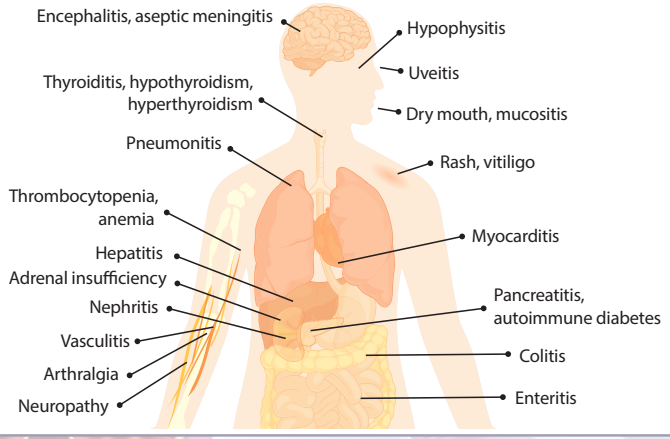
Immune checkpoint inhibitors are associated with important clinical benefits, but general immunologic enhancement can also lead to a unique spectrum of immune-related adverse events (irAEs)

Why do irAEs occur?

"Taking the brakes off" of the immune system can help the body fight cancer, but it can also lead to toxicity from a "supercharged" immune system.

What is the spectrum of potential irAEs?

Any organ system can be affected; commonly occurring are pulmonary (pneumonitis), dermatologic (rash, pruritus, blisters, ulcers, vitiligo), gastrointestinal (diarrhea, enterocolitis, transaminitis, hepatitis, pancreatitis), and endocrine (thyroiditis, hypophysitis, adrenal insufficiency) irAEs



How should irAEs be diagnosed and managed?

irAEs are often diagnosed by exclusion; other causes should be ruled out (including AEs of other therapies used), but immunotherapy-related toxicity should always be included in the differential

There should be a high level of suspicion that new symptoms are treatment related; early recognition, evaluation, and treatment of irAEs plus patient education are essential for best outcome

What are the general recommendations for management?

Depending on severity of irAEs, management may require corticosteroid or other immunosuppressive treatment as well as interruption or discontinuation of therapy

If appropriate, immunosuppressive treatment is used; patients generally recover from irAEs

Grade 1

Minimal or no symptoms; diagnostic changes only

- In general, checkpoint inhibitor therapy should be continued with close monitoring, with the exception of some neurologic, hematologic, and cardiac toxicities

Grade 2

Mild to moderate symptoms

- Hold checkpoint inhibitor therapy for most grade 2 toxicities
- Consider resuming immunotherapy when symptoms and/or laboratory values revert to grade 1 or lower
- Corticosteroids (initial dose of 0.5-1 mg/kg/d of prednisone or equivalent) may be administered

Grades 3/4

Severe or life-threatening symptoms

Grade 3 toxicities:

- Hold checkpoint inhibitor therapy
- Initiate high-dose corticosteroids (prednisone 1-2 mg/kg/d or methylprednisolone IV 1-2 mg/kg/d)
- If symptoms do not improve with 48-72 hours of high-dose corticosteroids, infliximab may be offered for some toxicities
- Taper corticosteroids over the course of at least 4-6 weeks
- When symptoms and/or laboratory values revert to grade 1 or lower, rechallenging with immunotherapy may be offered; however, caution is advised, especially in those patients with early-onset irAEs. Dose adjustments are not recommended

Grade 4 toxicities:

- In general, permanent discontinuation of checkpoint inhibitor therapy is warranted, with the exception of endocrinopathies that have been controlled by hormone replacement

Access the activity, "Chair's Take on Advances in Gynecologic Cancer Care: Exploring New Advances and Innovative Therapies in Endometrial and Cervical Cancers," at **PeerView.com/VSK40**

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Common adverse events associated with TKIs include diarrhea, fatigue, and hand–foot skin reaction[3,4]

Diarrhea[4]

For frequent, watery, bloody, or nocturnal stools, or any diarrhea or abdominal distress, patients should notify medical team immediately.

General Management

- ❑ Monitor bowel habits, and report any increase in activity above normal
- ❑ Avoid spicy or fatty foods; plain, simple foods are best
- ❑ Avoid fruit and caffeine
- ❑ Maintain adequate fluid intake to avoid dehydration
- ❑ Monitor/manage electrolytes

Medical Intervention

- ❑ Loperamide is usually effective
- ❑ If loperamide is ineffective, consider diphenoxylate/atropine

Hand–Foot Skin Reaction[5-7]

Symptoms

- ❑ Erythema with or without blisters; hyperkeratotic lesions on palms and soles
- ❑ Commonly accompanied by dysesthesia (burning, pain, tingling)

Prophylaxis

- ❑ Perform full-body skin examination, focusing on deformities and hyperkeratotic areas on palms and soles, before treatment initiation
- ❑ Have patients remove their shoes and examine their feet during each visit
- ❑ Recommend podiatrist evaluation (can help with removal of calluses and hyperkeratotic regions) and orthotist evaluation and use of orthotic devices in patients with abnormal weight bearing
- ❑ During early therapy (2-4 wk), encourage rest and avoidance of vigorous exercise and traumatic activity

Fatigue[4]

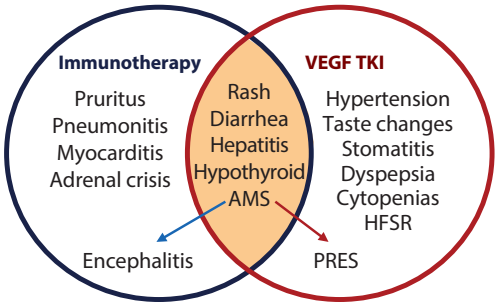
Educating your patients on managing fatigue is essential.

Patient Education

- ❑ Staying as active as possible helps regulate sleep
- ❑ Maintain a normal work and social schedule
- ❑ Take breaks as needed
- ❑ Tell your medical team if activity is intolerable or fatigue worsens

IO + TKI Combination Toxicities[8]

Be aware of overlapping toxicities that can occur with IO + TKI combination therapy.



ADL: activities of daily living; AMS: altered mental status; HFSR: hand–foot skin reaction; IO: immunotherapy; irAE: immune-related adverse event; PRES: posterior reversible encephalopathy syndrome; TKI: tyrosine kinase inhibitors.

1. Postow MA et al. *N Engl J Med.* 2018;378:158-168. 2. Brahmer JR et al. *J Clin Oncol.* 2018;36:1714-1768. 3. Walko CM et al. *Semin Oncol.* 2014;41(suppl 2):s17-s28. 4. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50. 5. McLellan B et al. *Ann Oncol.* 2015;26:2017-2026. 6. Brose MS et al. *Semin Oncol.* 2014;41(suppl 2):s1-s16. 7. Lacouture ME et al. *Oncologist.* 2008;13:1001-1011. 8. https://www.urotoday.com/conference-highlights/asco-gu-2020/asco-gu-2020-kidney-cancer/119282-asco-gu-2020-toxicity-profiles-and-side-effect-management-of-first-line-treatment-options-of-renal-cell-carcinoma.html.

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Immunotherapy in Endometrial and Cervical Cancer

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Selected Clinical Trials Assessing Immunotherapy in Cervical Cancer[3]

Phase 2

FDA Approved (PD-L1+)

Monotherapy Immunotherapy
NCT02628067: KEYNOTE-158
Pembrolizumab
Setting: 2L
Primary Endpoint: ORR

Dual Immunotherapy
NCT02488759: CheckMate -358
Nivolumab + Ipilumumab
Setting: 2L
Primary Endpoints: ORR, safety

Recruiting

Immunotherapy + PARP Inhibitor
NCT04068753: STAR
Dostarlimab + Niraparib
Setting: 2L
Primary Endpoint: ORR

Phase 3

Immunotherapy + Chemotherapy
NCT03635567: KEYNOTE-826
Pembrolizumab + chemotherapy vs
placebo + chemotherapy
Setting: 1L
Primary Endpoints: PFS, OS

Recruiting

Monotherapy Immunotherapy
NCT03257267: EMPOWER-Cervical 1
Cemiplimab vs
investigator's choice chemotherapy
Setting: 1L
Primary Endpoint: OS

Recruiting

Immunotherapy + Chemoradiotherapy
NCT03830866: CALLA
Durvalumab + SoC CCRT vs
placebo + SoC CCRT
Setting: 1L
Primary Endpoint: PFS

Recruiting

Chemotherapy + TKI ± Immunotherapy
NCT03556839: BEAT
cisplatin-paclitaxel + Bevacizumab
± Atezolizumab
Setting: 1L
Primary Endpoint: OS

Recruiting

Immunotherapy + Chemoradiotherapy
NCT04221945: KEYNOTE-A18
Pembrolizumab + CRT vs
placebo + CRT
Setting: 1L
Primary Endpoints: PFS, OS

CCRT: concurrent chemoradiotherapy; CTL: cytotoxic T lymphocytes; irAE: immune-related adverse event; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; TKI: tyrosine kinase inhibitor.

1. Wang D et al. *J Hematol Oncol*. 2019;12:42. 2. Makker V et al. 2019 American Society of Clinical Oncology Annual Meeting (ASCO 2019). Abstract TPS5607. 3. https://clinicaltrials.gov.

Access the activity, "Practical Perspectives on Rapid Change in Endometrial and Cervical Cancer Management: Exploring Innovative Therapy in Gynecologic Malignancies," at **PeerView.com/VSK40**