Endometrial Cancer: Enhancing the Patient Experience

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Case: Initial Presentation

A robust 72-year-old is referred to you after an episode of postmenopausal spotting

Endometrial biopsy reveals a grade 3 endometrioid adenocarcinoma of the uterus

She is otherwise asymptomatic and has no significant medical problems

Case : Surgery

Hysterectomy and lymphadenectomy

- Clinically enlarged pelvic and paraaortic nodes
- No gross residual disease at the completion of surgery

Final pathology:

- Grade 3 endometrioid adenocarcinoma 2 positive pelvic and 1 aortic node
- Pelvic and paraaortic nodes with extracapsular extension
- pMMR (IHC testing for MLH1, MLH2, PMS2, MSH6)
- P53 loss by IHC (mutated)
- Her2/neu and POLE not done

ARS: Options (assuming no clinical trial)

1. IV carboplatin/paclitaxel x 6
2. IV carboplatin/paclitaxel/bevacizumab x 6
3. IV carboplatin/paclitaxel x 6 followed by vaginal brachytherapy
4. Volume-directed chemo-XRT to pelvic/PAN followed by carboplatin/paclitaxel ×4
5. Pembrolizumab and lenvatinib

Case : Treatment

- ✓Staged IIIC2
- ✓IV carboplatin/paclitaxel x 6 followed by vaginal brachytherapy

Case: Recurrence and Treatment

- 13 months later: Elevated CA-125, back pain and radiologic progression in aortic and mediastinal nodes

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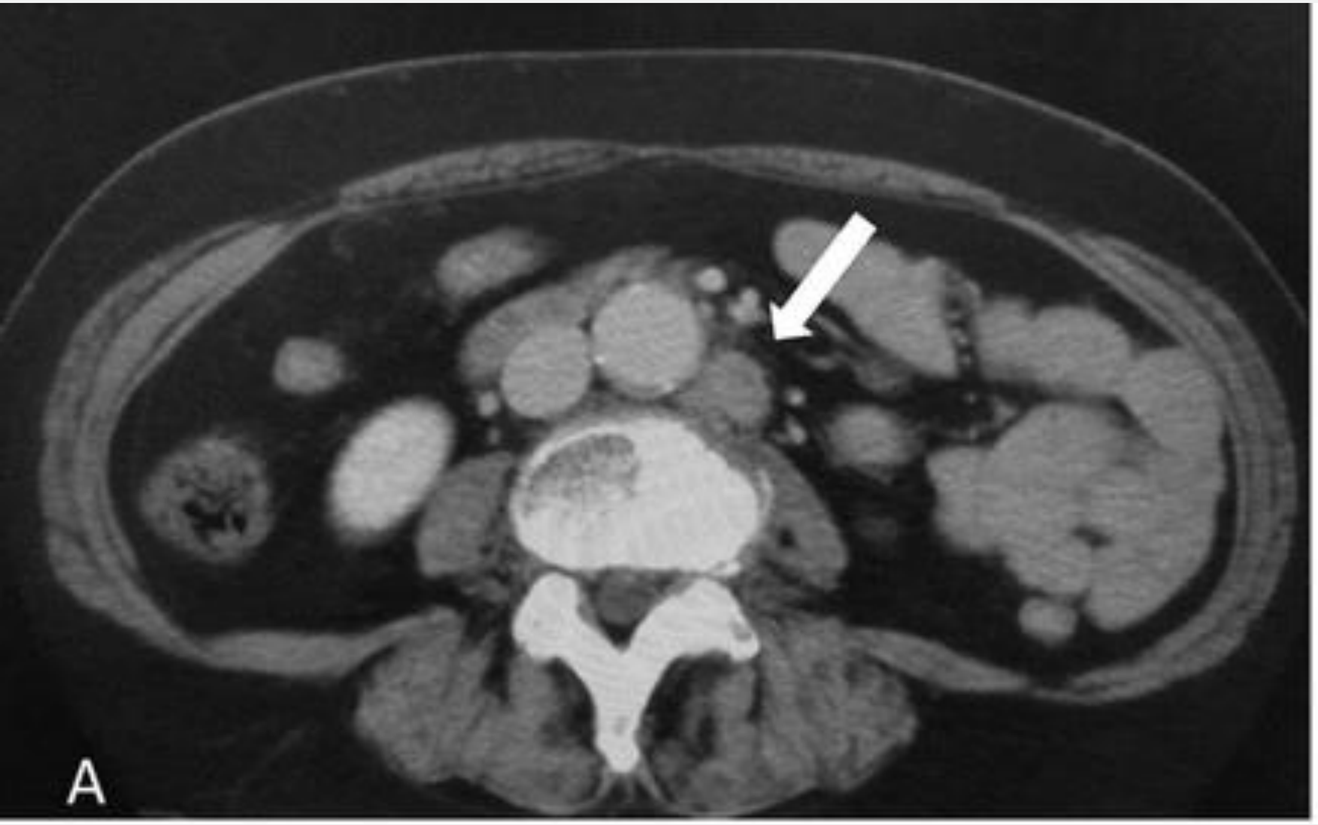
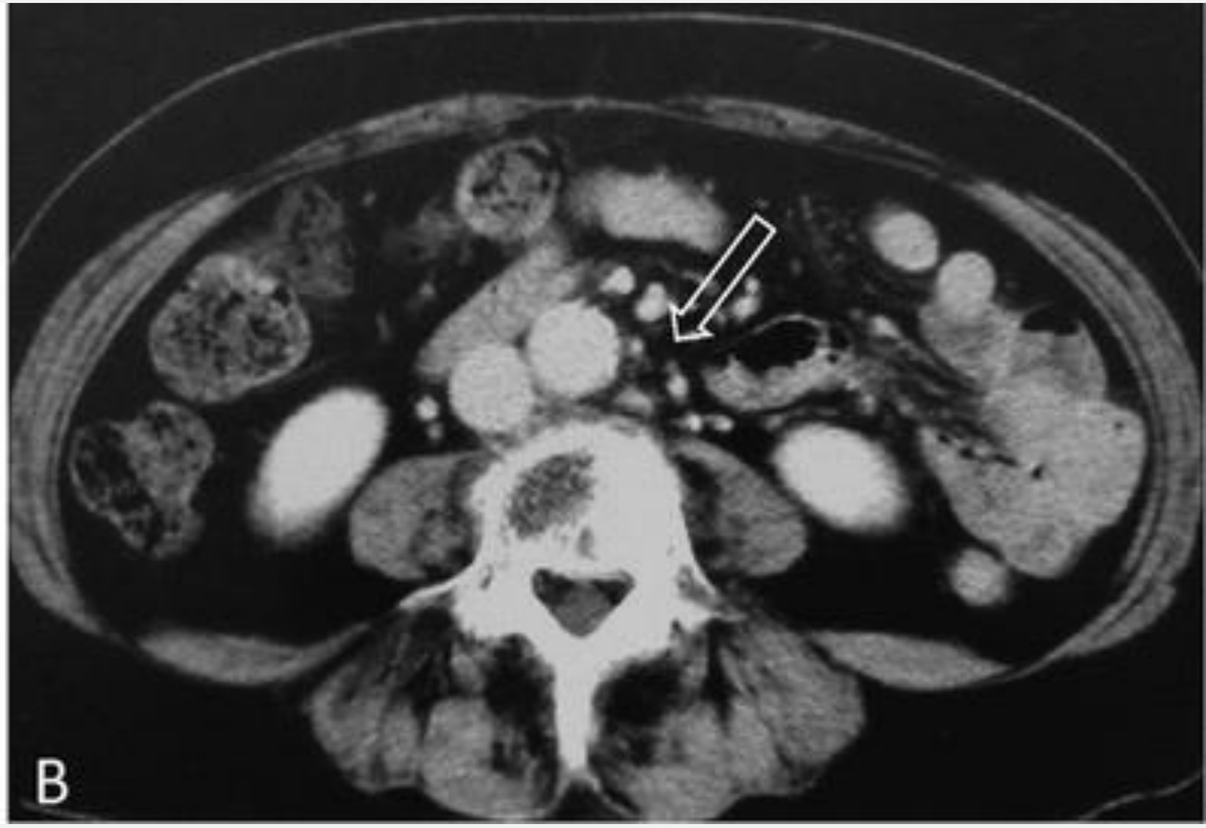
- Started on pembrolizumab every 3 weeks and lenvatinib (**20 mg**)
- First week: G-3 HTN controlled with lisinopril 10 mg qd
- 3rd week: Diarrhea managed with interruption and dose reduction to **14 mg**
  - 10 % decrease in weight
- 3rd month: G-2 Fatigue managed with interruption and dose reduction to **10 mg**

Case: Response





Baseline

After 12 weeks

Key's to Managing Endometrial Cancer 2-L ARs

- **<u>Single agent IO (Immune-related adverse events only)</u>**

- **<u>Combination IO + TKI</u>**

1) TKI related ARs
- GI (nausea, fatigue and weight loss)
- Fatigue

2) **Anti-angiogenic related ARs**
- HTN, proteinuria, thrombosis, bleeding, wound healing/fistula

3) Unique
- hypocalcemia, cardiac (QT interval prolongation, myocardial dysfunction), LFT

- Sorting out attributable agent is key (Diarrhea, LFTs, proteinuria)

TKI = Tyrosine kinase inhibitor
GI = Gastrointestinal
HTN = Hypertension
LFT = Liver function tests

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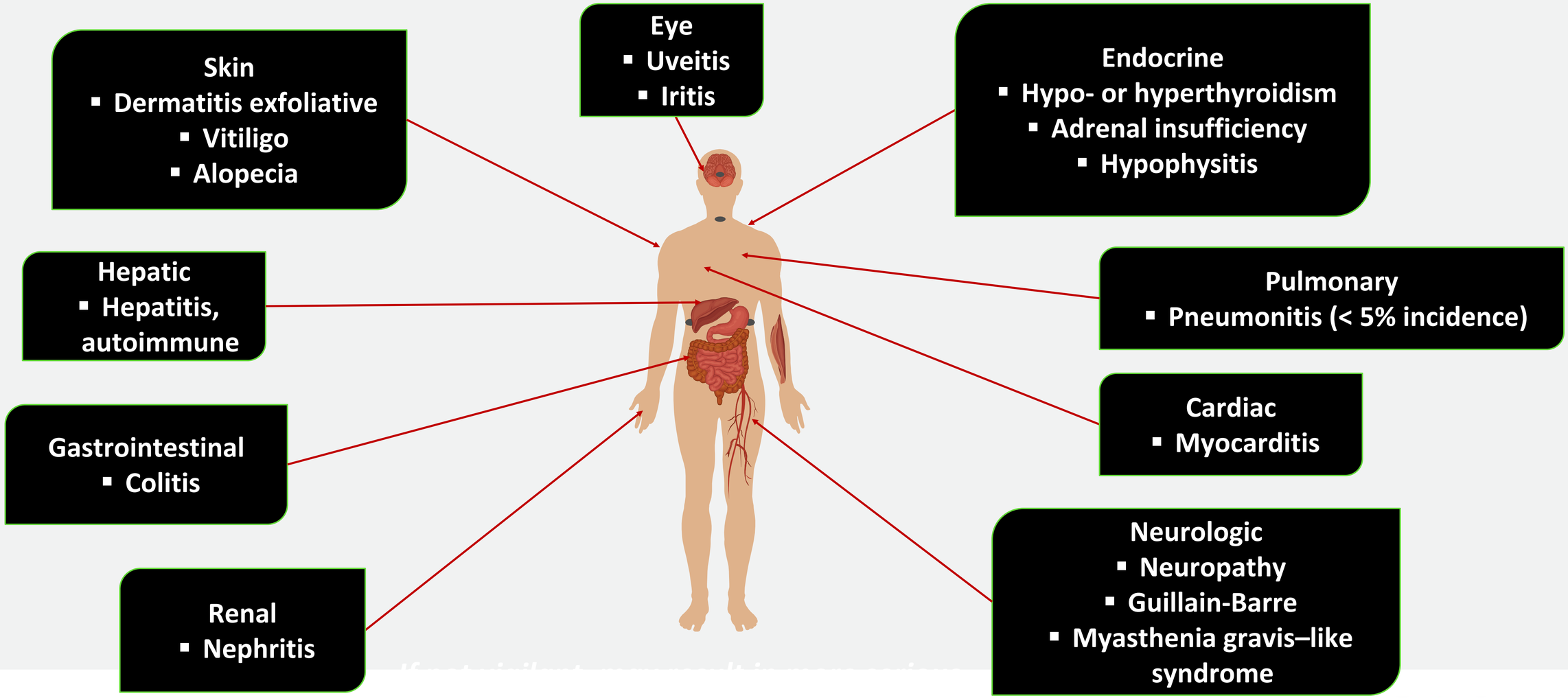
ARS: What Generally is the Most Common Immune Related AR Associated with Checkpoint Inhibitors

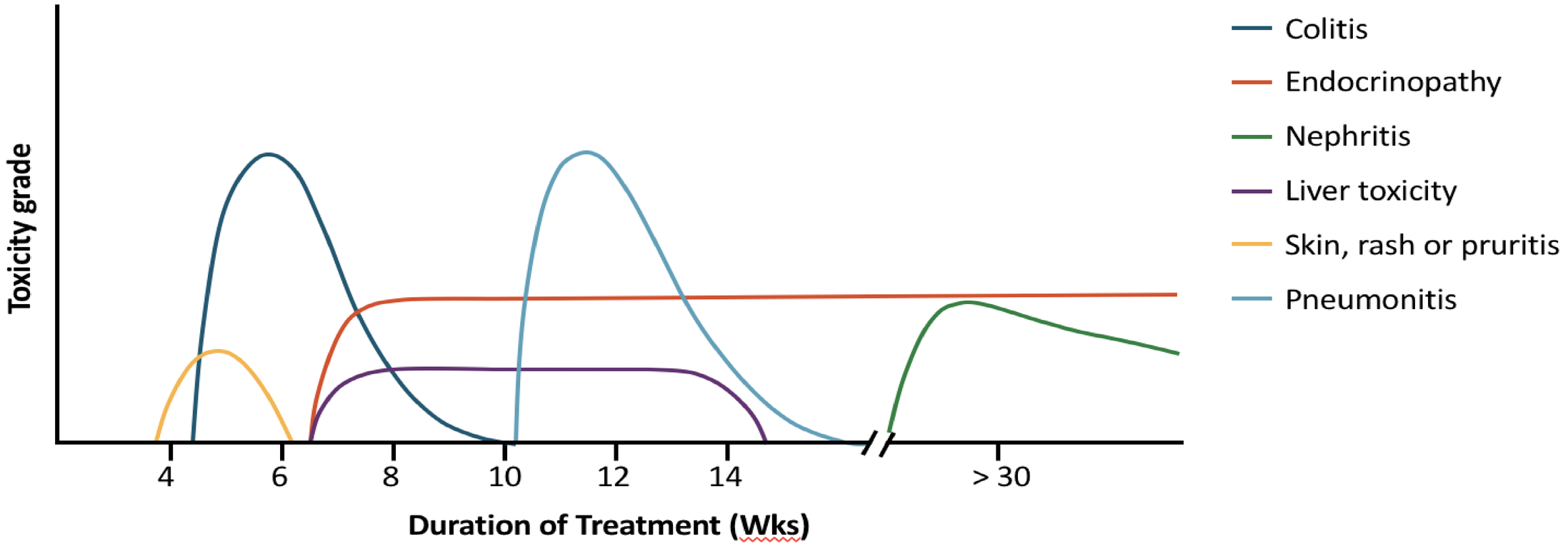
1. Hypothyroidism
2. Colitis
3. Pneumonitis
4. Nephritis
5. Hypophysitis

Immune-Related Reactions Events Can Affect Any Organ System



Brigden. Oncology Exchange. 2016;15:10-14.

Timing of irAR



Martins. Nat Rev Clin Oncol. 2019:16;563.

General Guidelines for Management of Immune-Related ARs

Grade 1: asymptomatic to mild symptoms

- Observation
- Intervention not needed

Grade 2: moderate symptoms

- Local or noninvasive intervention indicated
- Withhold drug, consider re-dose if toxicity resolves to grade ≤ 1
- Low-dose corticosteroids likely needed
- May be able to continue treatment

Grade 3: medically significant but not immediately life-threatening

- Stop immunotherapy immediately
- Hospitalization indicated
- High-dose steroids indicated
- Slow steroid taper over ≥ 1 mo once toxicity resolves to grade ≤ 1

Grade 4: life-threatening consequences

- Urgent intervention
- Permanently discontinue treatment

CTCAE v5.0. November 2017. Atezolizumab adverse reaction management brochure.
Nivolumab adverse reaction management guide. Pembrolizumab adverse reaction management guide.

Treatment of Severe irAR

Immunosuppression to reduce the excessive state of temporary inflammation

First line: steroids (methylprednisolone 1-2 mg/kg/d)

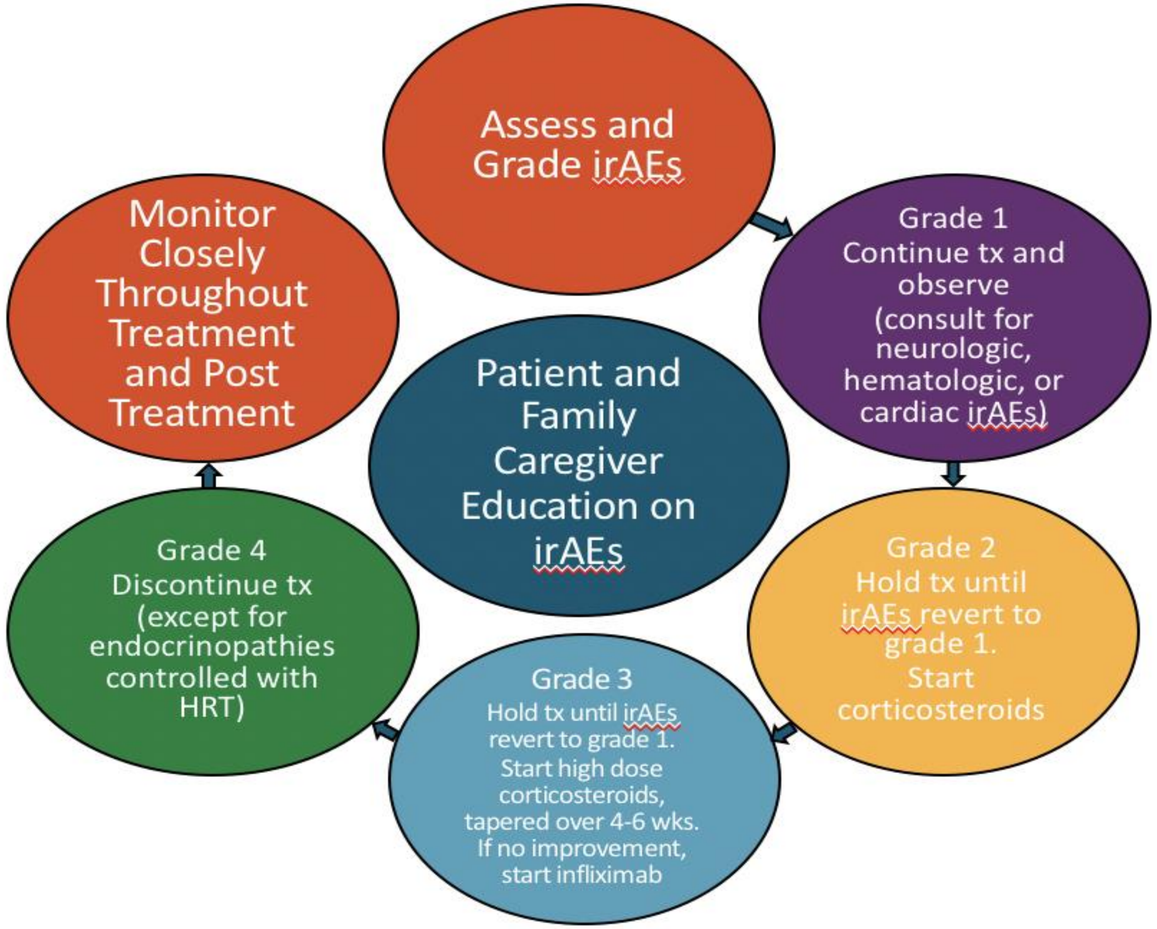
Additional immunosuppressive agents can be used if glucocorticoids are not initially effective

- Infliximab (Remicade, Renflexis, Inflectra)
- Mycophenolate mofetil (CellCept)

Hypothyroidism Grading & Management

Grade	Management
Grade 1: TSH <10 mIU/L and asymptomatic	- Continue therapy and close monitoring of TSH, FT4
Grade 2: Moderate symptoms; able to perform ADL; TSH >10 mIU/L	- Initiate TSH supplementation and monitor every 6-8 weeks while titrating
Grade 3-4: Severe symptoms, unable to perform ADLs	- Hold therapy until symptoms resolve to baseline - Endocrine consultation - Signs of myxedema: admit for IV therapy

Monitoring and Management of Immune-Related Adverse Events



Barber. Asia Pac J Oncol Nurs. 2019;3:212.

Principles of VEGFR-Targeted TKI Adverse Event Management

When reviewing the long list of potential ARs with patients, note that nobody gets all of them, but cannot predict which ones a given patient will experience

- Communication is key
- Must set expectations

See patient within 3 wks of starting treatment to detect emerging ARs early. When ARs emerge, low threshold to hold and restart at reduced dose

- Do not give up on agent altogether just because full dose isn't tolerated
- Do not continue until AEs become intolerable

For patients on combination treatment with immunotherapy, for AEs that are difficult to attribute (such as diarrhea), stop both drugs

- If AR resolves, attribute to TKI (short half life)
- If AR persists, attribute to immunotherapy

Relative Contraindications to Antiangiogenic Agents

1. Poor cardiac function or recent myocardial infarction
2. Uncontrolled hypertension
3. Large, unhealed wounds
4. History of colitis, diverticulitis, intestinal perforation, recent bowel surgery
5. Tumor invading trachea/esophagus/great vessels
6. Hemoptysis or unstable use of anticoagulants
7. Poor functional status and malnourished

Endometrial Cancer: Enhancing the Patient Experience

- ✓ Helping women love longer and better
- ✓ Setting expectations
- ✓ Close monitoring (phone calls, visits, labs, home monitoring including blood pressure)
- ✓ Appropriate interruptions and dose reductions
- ✓ Team approach

Thank You

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