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Positive Quality Intervention: Axitinib (Inlyta®) Plus Pembrolizumab (Keytruda ®) for Advanced Renal Cell Carcinoma

Description:

The purpose of this PQI is to provide information on the use of axitinib (Inlyta®) in combination with pembrolizumab (Keytruda ®) in the treatment of advanced renal cell carcinoma, as well as discuss clinical pearls to enhance appropriate patient selection, monitoring, and follow-up.

Background:

Axitinib is a tyrosine kinase inhibitor (TKI) that targets vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3 to reduce tumor angiogenesis and alter the tumor microenvironment.[1-3] Pembrolizumab is an immune checkpoint inhibitor (ICI) that blocks the PD-1 receptor, enhancing the immune system's ability to attack cancer cells.[4] Preclinical studies indicate that combining ICIs with anti-angiogenesis therapy is more effective than monotherapy, as it increases the anti-tumor immune cell ratio and decreases multiple immune checkpoint expressions.[2]

The combination of axitinib and pembrolizumab is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).[1] The combination is an NCCN category 1 recommendation for patients with relapsed or Stage IV clear cell RCC regardless of risk category.[5] Approval was based on the results of the phase III, randomized, open-label KEYNOTE-426 trial. At a median follow-up of 43 months, pembrolizumab plus axitinib vs. sunitinib showed a benefit in overall survival (46 mo vs. 40 mo; HR 0.73; 95% Confidence interval [CI], 0.6-0.88) and progression-free survival (16 mo vs. 11 mo; HR 0.68; 95% CI, 0.58-0.8).[4]

In combined therapies of axitinib with ICIs for advanced RCC, identifying overlapping toxicities such as diarrhea, hepatic toxicity, fatigue, and cardiovascular events is crucial for effective management.[6] Axitinib-related adverse events generally resolve within ≤ 3 days, potentially attributed to its short half-life (2.5-6.1 hours), facilitating quicker adjustments compared to other TKIs or when used with ICIs.[7,8] This rapid resolution helps distinguish between axitinib and immune-related toxicities, allowing for precise interventions such as temporary treatment interruption. Understanding these dynamics improves patient management, treatment adherence, and therapeutic outcomes.[9]

PQI Process:

Upon receipt of a new prescription of axitinib in combination with pembrolizumab:

- Verify the dose and indication and review chart notes to confirm combination therapy status
- Dosing
    - Axitinib initial dose: 5 mg orally every 12 hours with or without food
        - In patients with no adverse reactions > Grade 2 who are normotensive and not receiving antihypertensive medication may consider increasing dose at 6-week (or longer) intervals according to dosing schema in table below

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Table 1. Axitinib dose modifications

Dose Modification	Dose Regimen
Recommended starting dosage	5 mg every 12 hours
Dosage increase	
First dose increase	7 mg every 12 hours
Second dose increase	10 mg every 12 hours
Dosage reduction	
First dose reduction	3 mg twice daily
Second dose reduction	2 mg twice daily

    - Pembrolizumab: 200 mg IV over 30 minutes every 3 weeks or 400 mg IV over 30 minutes every 6 weeks; infusion rate may be reduced if mild or moderate infusion-related reactions occur[10]
- Treatment is continued until disease progression or unacceptable toxicity[1,10]
- Review medication list to screen for drug-drug, drug-food, drug-allergy, or drug-condition interactions
    - Strong CYP3A4/5 inhibitors: avoid use with axitinib if possible; if concomitant use cannot be avoided, then reduce axitinib dose by 50%[1]
    - Avoid strong CYP3A4/5 inducers with axitinib[11]
    - Grapefruit products and St John's wort: avoid use with axitinib[1]
    - Pregnancy/breastfeeding: verify negative pregnancy test prior to treatment and advise women of childbearing potential (and men taking axitinib with female sexual partners of reproductive potential) to use effective contraception during treatment and for 1 week after last axitinib dose (4 months after the last pembrolizumab dose); advise women not to breastfeed during treatment and for 2 weeks after last axitinib dose (4 months after last pembrolizumab dose)[1, 10]
- Ensure blood pressure is controlled (<150/100 mmHg) and left ventricular ejection fraction (LVEF) is > 50% prior to and during treatment[1]
    - If axitinib therapy is interrupted, monitor for patients on anti-hypertensive therapy for hypotension[12]
    - Optimize cardiovascular risk factors prior to and during treatment[12]
    - Monitor for thromboembolic or bleeding events during treatment[1]
- Obtain baseline CBC, CMP, thyroid panel, and urinalysis[1,10]
    - Re-evaluate CBC, CMP, thyroid panel, and urinalysis 2 weeks after initiation then as clinically indicated[9]
- Educate patient on proper perioperative medication management due to risk of impaired wound healing
    - Hold axitinib for at least 2 days prior to elective surgery; hold for 2 weeks for major surgery and until adequate wound healing occurs[1]

Patient-Centered Activities:

- Provide Oral Chemotherapy Education (OCE) and Intravenous Chemotherapy Education (IVE) sheets and review with the patient
- Instruct patient to monitor for immune-mediated adverse reactions (pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, dermatologic reactions); if severe hold treatment and initiate systemic corticosteroids[1,10,13]
- Ensure patient has access to antidiarrheal and urea-based emollient for prevention of palmar-plantar erythrodysesthesia (PPE)[9]
- Counsel patient on oral chemotherapy handling precautions
- Frequent patient follow-up at the beginning of treatment for the effective management of adverse events is critical to optimize adherence and improve clinical outcomes[9]

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Recommended Dosage Modification for Adverse Reactions for axitinib in combination with pembrolizumab[1]:			
Treatment	**Adverse Reaction**	**Severity**	**Dosage Modifications for axitinib**
Axitinib in combination with pembrolizumab	Liver enzyme elevations	ALT or AST at least 3 times ULN but less than 10 times ULN without concurrent total bilirubin at least 2 times ULN	• Withhold both axitinib and pembrolizumab until resolution to Grades 0–1 • Consider rechallenge with axitinib and/or pembrolizumab
		ALT or AST increases to more than 3 times ULN with concurrent total bilirubin at least 2 times ULN or ALT or AST at least 10 times ULN	• Permanently discontinue both axitinib and pembrolizumab
	Diarrhea	Grade 1–2	• Initiate symptomatic medications.
		Grade 3	• Interrupt axitinib and initiate symptomatic medications. If diarrhea is controlled, axitinib may be resumed at either the same dose or reduced by 1 dose level.
		Grade 4	• Withhold axitinib until resolution to Grade <2, then restart axitinib dose reduced by 1 dose level

Supplemental Information: Clinical Pearls

- Combination therapy has potential for overlapping toxicities; early identification of the underlying etiology of the toxicity is important for appropriate management strategies
  - Most common adverse events associated with axitinib therapy were diarrhea, fatigue, hypertension, nausea and PPE[12]
- Fatigue is a potential adverse event that can occur with both axitinib and pembrolizumab therapy
  - Closely monitor symptoms, consider holding treatment, and/or conduct endocrine assessments to help with management[1,10,12]
- Diarrhea is highly prevalent and usually occurs during the first 6 to 8 weeks of treatment[13]
  - Grade 1-2: initiate antidiarrheals
  - Grade 2 and greater: consider holding treatment and starting corticosteroids[1,10]
- Ensure patient is able to frequently self-monitor blood pressure for the first cycle, then periodically thereafter[9,13]
- Review prevalence and management strategies for common adverse events at Products and Diseases | US Medical Oncology (pfizerpro.com)

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