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Positive Quality Intervention: Cabozantinib (Cabometyx®)

Description: The purpose of this PQI is to provide a concise and comprehensive resource for proper medication management of patients utilizing Cabozantinib. Utilizing this resource should assist in decreasing medication toxicities and improving medication adherence and overall patient outcomes.

Background: Cabozantinib is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma (aRCC) as a first-line treatment in combination with nivolumab and as first and second-line monotherapy, patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib, and adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer (DTC) that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible.[1] The phase 3 METEOR trial examined aRCC patients treated with cabozantinib vs everolimus after ≥ 1 prior therapies. This study showed a median overall survival (mOS) of 21.4 months with cabozantinib vs 16.5 months with everolimus (HR 0.66, 95% CI 0.53–0.83; P = 0.0003).[2] Median progression free survival (mPFS) was 7.4 months vs 3.8 months (HR 0.58, 95% CI 0.45-0.74; < 0.0001). The phase 2 CABOSUN trial examined cabozantinib vs sunitinib in first-line aRCC. Median PFS was 8.6 months vs 5.3 months (HR 0.48, 95% CI 0.31-0.74, P = 0.0008). ORR was 20% vs 9% in the cabozantinib vs sunitinib arms, respectively.[4] The CheckMate-9ER trial examined cabozantinib plus nivolumab vs sunitinib in previously untreated aRCC patients. At final analysis, mPFS was 16.6 months in the combination treatment arm vs 8.3 months with sunitinib (HR 0.51, 95%CI 0.41-0.64), OS was 37.7 months vs 34.3 months (HR 0.70, 95% CI 0.55-0.90), and ORR was 55.7% vs 27.1% (P <0.0001).[1,5]
In HCC, the CELESTIAL trial evaluated cabozantinib vs placebo in post-sorafenib treated patients who had progressed on at least one prior systemic therapy. Median OS was 10.2 months vs 8 months (HR 0.76, 95% CI 0.63-0.92, P = 0.0049) and mPFS was 5.2 months vs 1.9 months (HR=0.44, 95% CI 0.36-0.52, P<0.0001).[6]
The COSMIC-311 trial evaluated second-line cabozantinib vs placebo in patients with metastatic DTC. In the cabozantinib arm, the mPFS was not reached compared to 1.9 months with placebo (HR 0.22, 95% CI 0.14-0.35, P<0.0001).[8]
The most common adverse effects of cabozantinib as a single agent include diarrhea, fatigue, palmar-plantar erythrodysesthesia (PPE), decreased appetite, hypertension, nausea, vomiting, decreased weight, and constipation. When given in combination with nivolumab: diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.[1]

PQI Process:
Upon the receipt of a new prescription of cabozantinib:

- Verify the dose and indication and review notes to identify combination therapy status
  - 40 mg daily on an empty stomach if combined with nivolumab
  - Target dose for monotherapy is 60 mg daily on an empty stomach
- Review patient medication list for possible drug-drug interactions
  - Strong 3A4 Inhibitors: Avoid if possible. If combined, decrease by 20 mg from desired dose
  - Strong 3A4 Inducers: Avoid if possible: If combined, increase by 20 mg from desired dose
  - Grapefruit and grapefruit juice: Avoid use
- Ensure blood pressure is controlled prior to initiation and that patient is capable of monitoring
  - Evaluate baseline cardiovascular risk
  - Ensure patient able to self-monitor daily BP for first cycle
  - ECG and Echo indicated for baseline in high or very-high cardiovascular risk patients
- Obtain baseline CBC with diff, CMP including magnesium and phosphorus, thyroid panel
  - Re-evaluate CMP, CBC w/ diff 2 weeks after initiation and as clinically indicated

    - Re-evaluate thyroid function every 4 weeks for 4 months, then every 2-3 months
- Education patient on proper perioperative medication management
    - Hold 3 weeks prior and 2 weeks after any major surgery (including invasive dental procedures)
- Coordinate with treatment team to establish start date of therapy
    - If combined with nivolumab, staggered initiation may allow differentiation of adverse reactions

Patient-Centered Activities:

- Provide Oral Chemotherapy Education (OCE) sheet and review with patient
- Consider providing Treatment Support Kit (TSK)
- Instruct patient on proper blood pressure monitoring technique and to report any increases from baseline
    - Coordination provision of home BP monitor if needed
- Ensure patient has access to antidiarrheals and antiemetics prior to start of therapy
- Counsel patient on identification of dermatologic toxicities and proper skin care recommendations
    - Use of Urea-based emollient for prevention of hand-foot skin reaction
- Establish accessible and direct communication with clinical pharmacy team
    - Reporting issues for early management can prevent therapy interruptions
    - Frequent outreach necessary in early stages of therapy to manage toxicities

Dose Modifications for Adverse Reactions: [1]

Adverse Reaction	**Severity**	**Dose Modification**
GI toxicity: Diarrhea	Any	Manage with antidiarrheals, **see supplemental information**
	Grades 2, 3, 4	Withhold therapy until ≤ Grade 1. Resume at reduced dose
GI toxicity: perforation or fistula	Any	Permanently discontinue
Hemorrhage	Any	Permanently discontinue
Hypertension	Grade 3	Withhold therapy until ≤ Grade 2, and resume at lower dose. Manage with antihypertensives per guidelines
	Grade 4	Permanently discontinue
	Hypertensive Crisis	Permanently discontinue
Hypocalcemia	Any	Replace calcium as necessary, evaluate need for hold or dose reduction
Osteonecrosis of the jaw	Any	Withhold therapy until resolution. Resume at reduced dose
Palmer-planter erythrodysethesia	Grade 2/3	Withhold therapy until ≤ Grade 1. Resume at reduced dose
Reversible posterior leukoencephalopathy syndrome	Any	Permanently discontinue
Thromboembolic Events	Acute MI, VTE (grade 4), ATE (Grade 3/4), CVA (Grade ≥2)	Permanently discontinue
Other adverse reactions	Grade 2 (intolerable), Grades 3 or 4	Withhold therapy until ≤ grade 1. Resume at reduced dose

Supplemental Information: Clinical Pearls

- Diarrhea is highly prevalent and occurs in first few weeks of cabozantinib therapy[9]
    - Important to differentiate from immunotherapy
    - Treatment diary may assist in identification of lifestyle or dietary triggers
    - Loperamide, diphenoxylate/atropine, tincture of opium, octreotide
    - Small frequent meals and incorporation of BRAT diet

- Dermatologic toxicities are common and can impact quality of life for first 8 weeks of therapy[10]
    - Acneiform rash is best managed with topical corticosteroids
    - May consider prophylactic oral antibiotic, sun precautions, and topical corticosteroid
    - VEGF-PPE occurs early, localized to pressure points, appearing as painful and callus-like
        - Prophylaxis with urea-based emollient and emphasis to avoid localized trauma
- Cabozantinib has a half-life of approximately 99 hours and upon dose hold AEs generally begin to resolve within days
- Alternative treatment schedules assist in balancing efficacy and tolerability and increase PFS[11]
    - Clarifying to patients that dose reductions may not have clinical impact on efficacy
    - Personalize method to maximize tolerability and increase likelihood of insurance coverage
        - ie: 40/60mg alternating schedule, 7 on: 1 off
    - Patients may exhibit prodromal symptoms prior to severe ADRs which may be improved by a single dose hold
        - May provide opportunity for individualization of treatment regimen
        - Emphasis on obtaining highest tolerable average weekly dose

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