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Positive Quality Intervention: Sorafenib (Nexavar®) for the Treatment of Hepatocellular Carcinoma and Transition to Second-line Regorafenib (Stivarga®)

Description: This PQI will discuss effective management of adverse effects of sorafenib in the treatment of hepatocellular carcinoma and discuss data supporting the sequencing of patients to second-line therapy with regorafenib for increased survival benefit.

Background: Hepatocellular carcinoma (HCC) is associated with a high mortality rate and historically the treatment options have been limited. Prior to 2018, sorafenib was the only Food and Drug Administration approved targeted therapy for the initial treatment of unresectable HCC in patients diagnosed with late stage or metastatic disease.[1] Second-line treatment options, though growing in number, have limited and at times conflicting survival data; and all factors of options should be considered.[2,3] A retrospective study of the RESORCE trial ascertained median time from start of sorafenib to death in patients receiving sequential therapy to regorafenib. Exploratory analysis revealed time from sorafenib initiation to death as 26 months for regorafenib patients vs. 19.2 months for placebo patients (HR (95% CI) 0.44 (0.36–0.54)).[3] Sorafenib is a first line options for select patients with HCC Child-Pugh Class A or B7.[4]

PQI Process: Upon receipt of a prescription for sorafenib[5]

- Obtain CBC with differential, metabolic panel including magnesium and phosphorus, liver function tests, lipase and amylase prior to starting therapy and then monthly until labs have stabilized
- Check for drug interactions: Strong CYP3A4 inducers
- Obtain thyroid labs at baseline, every 4 weeks for 4 months, and then every 2-3 months thereafter
- Monitor blood pressure at baseline and weekly during the first 6 weeks of sorafenib, and then monitor blood pressure, utilizing clinic appointments and treat any developing hypertension as needed
- Treatment associated hypertension and dermatologic toxicity are managed with dose interruptions and reductions[8] (Grade 1 dermatologic toxicity may not require dosage adjustments) (see Table 3)
- Dose adjustments for baseline hepatic and renal dysfunction have been recommended based on a phase I pharmacokinetic study and are included in Table 1 and 2[6]
- Consider proactively discussing 2nd line treatment options following progression or intolerance; if regorafenib is considered for 2nd line tyrosine kinase inhibitor transitioning
    - Ensure recovery from sorafenib mediated adverse effects and that patient did not permanently discontinue sorafenib due to toxicity or inability to tolerate doses
    - Determine Child-Pugh Class status and make appropriate recommendation for therapy
    - If underlying hypertension exists or developed while on sorafenib, ensure appropriate blood pressure control prior to starting regorafenib
    - Refer to Regorafenib (Stivarga®) In the Treatment of Hepatocellular Carcinoma PQI

Patient-Centered Activities:

- Provide patient on sorafenib Oral Chemotherapy Education (OCE) Sheet
- Counsel patient on the signs and symptoms of hand-foot syndrome (Medication Induced Hand-Foot Syndrome)
- Counsel on appropriate management of diarrhea (Oncolytic Induced Diarrhea and Oral Chemotherapy Education Supplemental)
- Counsel on measuring blood pressure weekly at home and to report blood pressure > 140/90 mmHg
- If changing regorafenib provide patient Oral Chemotherapy Education (OCE) Sheet and Oral

Chemotherapy Education Supplemental Sheet

Supplemental Information:

Table 1: Dose Adjustments for Baseline Hepatic Dysfunction[6*]

Degree of Hepatic Impairment	Criteria	Sorafenib Dose
Mild	Bilirubin >1 to ≤1.5 times ULN and/or AST >ULN	400 mg twice daily
Moderate	Bilirubin >1.5 to ≤3 times ULN; any AST	200 mg twice daily
Severe	Albumin <2.5 g/dL with any bilirubin/AST	200 mg once daily
	Bilirubin >3 to 10 x ULN with any AST	No tolerable dose identified

*Reference used differs slightly from sorafenib prescribing information reference

Table 2: Dose Adjustments for Baseline Renal Dysfunction[6]

Baseline Creatinine Clearance	Sorafenib Dose
40-59 mL/min	400 mg twice daily
20-39 mL/min	200 mg twice daily
< 20 mL/min	Unable to define dose
Hemodialysis	200 mg once daily

Table 3: Dose Reduction Levels for Adverse Effects

Dose Reduction	Sorafenib Dose
Starting	400 mg twice daily
1	400 mg once daily
2	200 mg once daily or 400 mg every other day
3	Discontinue

References:

1. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359:378-390.
2. Merck Provides Update on KEYNOTE-240, a Phase 3 Study of KEYTRUDA® (pembrolizumab) in Previously Treated Patients with Advanced Hepatocellular Carcinoma. Merck. Published February 19, 2019. https://bit.ly/2SQ6J45.
3. Finn RS et. Al Outcomes of sequential treatment with sorafenib followed by regorafenib for HCC. J Hepatol. 2018 Aug;69(2):353-358.
4. NCCN Guidelines Retrieved September 13, 2022, from https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf.
5. Nexavar® [package insert].
6. Miller AA, Murry DJ, Owzar K, et al. Phase I and pharmacokinetic study of sorafenib in patients with hepatic or renal dysfunction. JCO. 2009 Apr;27(11):1800-5.