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Positive Quality Intervention: Trifluridine and Tipiracil (Lonsurf®) for Metastatic Colorectal Cancer

Description: This PQI will highlight strategies for appropriate dosing and management of adverse effects related to trifluridine-tipiracil treatment in metastatic colorectal cancer.

Background: Trifluridine and Tipiracil is indicated for the treatment of patients with metastatic colorectal cancer as a single agent or in combination with bevacizumab who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy (anti-EGRF therapy should not be used in right sided tumors).[1] This has been designated as a category 2A by NCCN.[2] The RECOURSE trial showed a survival benefit of 7.1 months (trifluridine and tipiracil) versus 5.3 months (placebo).[3] Grade 3 and greater adverse effects occurred due to neutropenia (38%), decreased appetite (4%), diarrhea (3%) and nausea/vomiting (2%). Trifluridine and Tipiracil in combination with bevacizumab has also been studied in the non-first-line setting in the C-TASK FORCE study. After a 10 month median follow-up, median progression free survival was 2.6 months with trifluridine and tipiracil alone, compared to 4.6 months in combination with bevacizumab.[4] Toxicities were similar between with two groups. The SUNLIGHT trial investigated the efficacy and safety of trifluridine/tipiracil plus bevacizumab versus trifluridine/tipiracil alone in patients with refractory mCRC following disease progression or intolerance on two prior chemotherapy regimens. Results from the main analysis demonstrated that the investigational combination provided a statistically significant and a clinically meaningful improvement in OS of 3.3 months compared to trifluridine/tipiracil alone (10.8 months vs. 7.5 months, hazard ratio [HR]: 0.61, 95% confidence interval [CI]: 0.49-0.77, $p<0.001$).[5] A total of 29.3% of patients in the trifluridine/tipiracil plus bevacizumab and 19.5% trifluridine/tipiracil alone received G-CSF support. All patients, regardless of their baseline disease characteristics, sidedness of tumor, RAS mutational status, stratification factors or prior exposure to bevacizumab benefitted from trifluridine/tipiracil plus bevacizumab therapy vs trifluridine/tipiracil monotherapy. Trifluridine and Tipiracil is indicated for the treatment of patients with gastric cancer (see Trifluridine and Tipiracil (Lonsurf®) for Treatment of Gastric Cancer PQI).

PQI Process[1]: Upon receiving a prescription for trifluridine and tipiracil

- Verify the correct dose
  - 35 mg/m^2 based on trifluridine component (maximum 80 mg or 160 mg/day) orally twice daily within 1 hour of a meal on days 1- 5, and days 8 - 12, repeated every 28 days until disease progression or unacceptable toxicity
    - Round to the nearest 5 mg increment
    - Absence of food does not affect AUC but can cause CMAX spike and adverse effects
    - It is not recommended to start at a lower dose to prevent dose limiting toxicities
  - Bevacizumab 5 mg/kg on days 1 and 15 (if applicable)
- Obtain complete blood counts prior to Day 1 and on Day 15 of each cycle
  - Make sure platelets are ≥ 75,000/mm^3 and ANC > 1500mm^3 prior to the start of each cycle
- Check liver function
  - Do not initiate therapy in patients with moderate to severe hepatic impairment (Bilirubin >1.5 ULN and any AST elevation)
- Check renal function
  - CrCl 15-29: Reduce to 20 mg/m^2 orally two times daily
    - Consider reduction to 15 mg/m^2 orally two times daily if further reduction is needed
- Withhold trifluridine and tipiracil for any of the following

    - Absolute neutrophil count (ANC) less than 500/mm^3 or febrile neutropenia
    - Platelets less than 50,000/mm^3 or Grade 3 or 4 non-hematological adverse reactions
    - After recovery, resume after reducing the dose by 5 mg/m^2/dose from the previous dose level for the following only if there is more than a week delay of the next cycle
        - Febrile neutropenia
        - Uncomplicated Grade 4 neutropenia (recovered to ≥1,500/mm^3) or thrombocytopenia
- Timing of presentation of adverse events
    - Cycles 1-3 are the cycles with the highest incidence of adverse events
    - Neutropenia
        - Dose holidays are preferred for neutropenia
        - Retrospective data shows neutropenia at the 1-month mark showed trend towards overall survival benefit[2]

Patient-Centered Activities:

- Provide Oncology Chemotherapy Education (OCE) sheet and counsel on potential side effects
- Counsel patient on dosing schedule and administration
    - Consider starting on a Monday to complete days 1-5 from Monday to Friday, break on the weekend (days 6-7), and resume Monday to Friday for days 8-12; no medication on days 13-28
    - Notify the patient that dose delays may be beneficial when managing adverse effects, and should not interfere with their ability to receive treatment or achieve benefit
- Provide medication calendar and clinic appointments calendar
- Ensure patient has access to at home antiemetic and antidiarrheal medications
- Counsel patient on safe storage, handling, and disposal of cytotoxic drugs (wear gloves)
- Provide Lonsurf® Starter Kits contain patient and caregiver brochures, pillboxes, and thermometer
- Patient Assistance: NCODA Financial Assistance Tool

References:

1. Lonsurf® (trifluridine/tipiracil) [package insert].
2. NCCN Clinical Practice Guidelines in Oncology (NCCN guidelines®) for colon cancer.
3. Atsushi Ohtsu, Takayuki Yoshino, et. Al On Behalf of the RECOURSE Study Group. Onset of neutropenia as an indicator of treatment response in the phase 3 RECOURSE trial of trifluridine/tipiracil (TAS-102) versus placebo in patients with metastatic colorectal cancer. Journal of Clinical Oncology 2017 35:4_suppl, 775-775.
4. Pfeiffer P, Yilmaz M, Möller S, et al. TAS-102 with or without bevacizumab in patients with chemorefractory metastatic colorectal cancer: an investigator-initiated, open-label, randomised, phase 2 trial. Lancet Oncol 2020;21:412-420.
5. 2023 ASCO Gastrointestinal Cancers Symposium. In *Abstract #392020 SUNLIGHT trial: Overall Survival Data for Trifluridine/Tipiracil (LONSURF®) In Combination With Bevacizumab in Patients With Refractory Metastatic Colorectal Cancer* . San Francisco.

Supplemental Information:

Dosing According to Body Surface Area[1]: (dosage calculator and calendar creator)

BSA (m^2)	Total daily dose (mg)	Dose (mg) administered twice daily	Tablets per dose	
			15 mg	20mg
<1.07	70	35	1	1
1.07 – 1.22	80	40	0	2
1.23 – 1.37	90	45	3	0
1.38 – 1.52	100	50	2	1
1.53 – 1.68	110	55	1	2
1.69 – 1.83	120	60	0	3
1.84 – 1.98	130	65	3	1
1.99 – 2.14	140	70	2	2
2.15 – 2.29	150	75	1	3
≥ 2.30	160	80	0	4