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Positive Quality Intervention: Trifluridine/Tipiracil (Lonsurf®) for Treatment of Gastric Cancer

Description: This PQI will review patient identification and clinical considerations for trifluridine/tipiracil treatment option for gastric cancer.

Background: Trifluridine/tipiracil is approved for use in patients with gastric or gastroesophageal junction (GEJ) cancer who have failed at least two prior lines of chemotherapy including a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy.[1] This approval is based on results from the TAGS trial, a Phase III, multinational, randomized, double-blind trial that compared trifluridine/tipiracil plus best supportive care vs. placebo plus best supportive care in metastatic GEJ/gastric cancer patients previously treated with at least 2 prior regimens. Median overall survival was 5.7 months (95% CI 4.8–6.2) in the trifluridine/tipiracil group and 3.6 months (3.1–4.1) in the placebo group.[2] Sequencing of treatment in advanced gastric cancer is still not well defined, but trifluridine/tipiracil serves as a viable option for 3rd and subsequent lines of treatment and is currently NCCN category 1 recommended for 3rd line (or later) therapy.[3] Trifluridine and Tipiracil is also indicated for the treatment of patients with metastatic colorectal cancer as a single agent or in combination with bevacizumab (see **Trifluridine and Tipiracil (Lonsurf®) for Metastatic Colorectal Cancer** PQI).

PQI Process: 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 to spike leading to 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 greater than or equal to 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[4]

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 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 support kit - 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. Shitara K. et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2018 Nov;19(11):1437-1448. doi: 10.1016/S1470-2045(18)30739-3.
3. NCCN Guidelines Gastric Cancer.
4. 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.

Supplemental Information:

Dosing According to Body Surface Area[1]: (dosage calculator and calendar creator at http://www.lonsurfhcp.com/dosing/dosage-calculator)

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