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Positive Quality Intervention: Zolbetuximab (Vyloy®) for Gastroesophageal Cancers

Description: This PQI will discuss clinical information regarding zolbetuximab in the management of patients with gastroesophageal cancers and to provide insights into best clinical practices.

Background:
Zolbetuximab is a first-in-class chimeric immunoglobulin monoclonal antibody that binds to claudin 18.2 (CLDN18.2), a tight junction protein normally expressed in gastric mucosa but aberrantly expressed on the surface of gastroesophageal junction (GEJ) and gastric adenocarcinoma cells.

Zolbetuximab is indicated in adult patients as follows:

- In combination with fluoropyrimidine- and platinum containing chemotherapy for first-line treatment of human epidermal growth factor receptor 2 (HER2)-negative, locally advanced unresectable or metastatic GEJ or gastric adenocarcinoma whose tumors are CLDN 18.2 positive

Most common adverse reactions (≥15%) in combination with mFOLFOX or CAPOX:

- Nausea, vomiting, diarrhea, abdominal pain, constipation, fatigue, peripheral sensory neuropathy, hypersensitivity reactions, pyrexia, appetite and weight loss
  - In a combined analysis of the SPOTLIGHT and GLOW trials, the incidence of nausea decreased between cycles 1 and 2 of therapy (58% vs. 18%) as did the incidence of vomiting (43% vs. 15%)[3].
- Most common laboratory abnormalities (≥15%):
  - Decreased: neutrophil count, leukocyte count, lymphocyte count, hemoglobin, platelets, glucose, albumin, sodium, potassium, magnesium
  - Increased: creatinine, glucose, AST/ALT, Alk phos, phosphate

PQI Process:

1. **Eligibility Assessment and Clinical Criteria Confirmation:**
   a. **Provider:**
      i. Confirm the diagnosis of HER2-negative GEJ or gastric adenocarcinoma which is locally advanced unresectable or metastatic that is previously untreated
      ii. Confirm CLDN18.2 positivity defined as ≥ 75% of tumor cells demonstrating moderate (2+) to strong (3+) membranous CLDN18 IHC staining using the approved companion VENTANA CLDN18 (43-14A) RxDx Assay
      iii. Assess ECOG performance status to ensure appropriateness for combination chemotherapy (CAPOX or FOLFOX) and zolbetuximab
      iv. If baseline nausea and/or vomiting symptoms are present, it is recommended to resolve these to Grade ≤ 1 prior to administering zolbetuximab

2. **Dosage Determination and Ordering**
    a. **Provider:** Determine the appropriate dosing, place orders, and schedule patient
        i. Order zolbetuximab in combination with fluoropyrimidine (5-fluorouracil or capecitabine) and platinum-containing chemotherapy (oxaliplatin)
            - Starting dose: 800 mg/m^2 for the first dose
            - Subsequent doses of 600 mg/m^2 every 3 weeks or 400 mg/m^2 every 2 weeks.
        ii. Acknowledge the estimated minimum infusion time for the first zolbetuximab infusion is approximately 3.5 hours and that for subsequent infusions is about 2.5 hours with the total infusion times depending on dose interruptions or infusion rate reductions
        iii. If zolbetuximab and chemotherapy are administered on the same day, zolbetuximab must be administered first
        iv. Zolbetuximab is highly emetogenic. Order premedications for nausea/vomiting prevention with a combination of antiemetic medications to be given prior to each dose
            - Sample emesis prevention regimen: olanzapine + NK1 receptor antagonist + 5-HT3 receptor antagonist + dexamethasone[5]
        v. There are no known recommendations for dose adjustments for zolbetuximab based on renal or hepatic function
    b. **Pharmacist:** Verify dose accuracy in electronic health record and confirm consistency with clinical guidelines
3. **Patient Education and Counseling:**
    a. **Provider/Pharmacist:** Provide comprehensive education on zolbetuximab with emphasis on:
        i. Risk of severe nausea/vomiting which occurs more often during the first treatment. Counsel on antiemetic use
        ii. Monitoring for hypersensitivity reactions and the possible need for in-clinic monitoring after completing the zolbetuximab infusion
            - If clinically indicated, patients should be monitored for 2 hours after the completion of the infusion or longer.
            - This observation period after the infusion is a recommendation (not a requirement) based upon clinician's judgement.
            - If chemotherapy is being given on the same day, monitoring can happen while continuing with chemotherapy infusion
        iii. Ensuring patients have anti-emetic prescription approvals so they are readily available and educating patients to take them as advised keeping in mind that patients will also be receiving chemotherapy, which is also emetogenic
            - Median time to onset of nausea/vomiting is < 1 hour after initiation of first zolbetuximab infusion. Occurrences of nausea or vomiting are most common during the first zolbetuximab infusion and decrease with subsequent infusions.
        iv. Advising pregnant women of women of child-bearing potential that there are no data on the use of zolbetuximab in pregnancy to inform any drug-associated risks

v. Advising lactating women they should not breast feed during treatment with zolbetuximab and for 8 months after the last dose

4. **Drug Interaction Evaluation:**
   a. **Pharmacist:** There are no known drug interactions with zolbetuximab as it is catabolized into small peptides and amino acids.
5. **Drug Dispensing**
   a. **Provider/Pharmacist/Infusion Nursing:**
      i. Administering zolbetuximab
         - Premedicate with combination of antiemetics prior to each infusion
         - 1st dose zolbetuximab 800 mg/m^2: infuse at 100 mg/m^2/hour for the first 30-60 minutes and increase rate to 200-265 mg/m^2/hour thereafter in the absence of adverse reactions as tolerated
            a. In-line filter use recommended during administration
         - Subsequent doses:
            a. If using zolbetuximab 600 mg/m^2 every 3-week dosing: infuse at 75 mg/m^2/hour for the first 30-60 minutes and increase rate to 150-265 mg/m^2/hour thereafter in the absence of adverse reactions as tolerated
            b. If using zolbetuximab 400 mg/m^2 every 2-week dosing: infuse at 50 mg/m^2/hour for the first 30-60 minutes and increase rate to 100-200 mg/m^2/hour thereafter in the absence of adverse reactions as tolerated
      ii. If zolbetuximab and chemotherapy are administered on the same day, zolbetuximab must be administered first
6. **Adverse Event Management**
   a. There are no dose reductions for zolbetuximab, and adverse reactions are managed by reducing the infusion rate, interruption of infusion, withholding the dose, or permanently discontinuing zolbetuximab
   b. Hypersensitivity reaction or infusion related reaction management:
      i. If grade 2 reactions (moderate), interrupt the infusion until recovery to ≤ grade 1 (mild) and resume infusion at a reduced rate for the remaining infusion. Premedicate with antihistamines for future doses and run at slower rates, gradually increasing rate as tolerated.
      ii. If anaphylaxis or grade 3/4 reactions (severe but not immediately life-threatening or life-threatening), immediately stop and permanently discontinue zolbetuximab, treat symptoms according to standard management, and monitor until symptoms resolve.
   c. Severe nausea/vomiting management:
      i. Premedicate with antiemetics prior to each infusion
      ii. If grade ≥ 2 nausea, interrupt infusion until recovered to grade ≤ 1 and resume infusion at reduced rate for remaining infusion
      iii. If grade 2 or 3 vomiting, interrupt infusion until recovered to grade ≤ 1 and resume infusion at reduced rate for remaining infusion
      iv. Manage with antiemetics and fluids as needed and premedicate the next infusion
      v. If grade 4 vomiting, immediately stop and permanently discontinue zolbetuximab

d. Monitor for dehydration and electrolyte abnormalities as sequelae to nausea/vomiting. Replace fluids and electrolytes as appropriate
e. Refer to the consensus guidance for prevention and management of nausea and vomiting in patients treated with zolbetuximab + chemotherapy Delphi panel study for further guidance in titrating zolbetuximab dose in patients experiencing nausea and/or vomiting during infusion[4]

7. **Patient Centered Activities:**
   a. Provide patients with a patient information sheet or equivalent educational material that explains zolbetuximab's purpose, dosing, side effects, and important safety information.
   b. Counseling pearls:
      i. Advise patients on the risks of nausea/vomiting and to alert their nurse if they begin to experience GI upset during infusion. Reinforce the importance of patient compliance to antiemetics and that the chemotherapy they're recieving can also cause nausea
      ii. Advise patients on the risks of hypersensitivity reactions and the potential need for in-house monitoring after completion of zolbetuximab infusion
         - If chemotherapy is being given on the same day, monitoring can happen while continuing with chemotherapy infusion
      iii. Advise patients on the risks of nausea/vomiting which are highest during the first infusion and decrease with subsequent infusions, and counsel them on aggressive anti-emetic management for immediate or delayed nausea at home
      iv.

References

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