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Positive Quality Intervention: Oral Formulation of Decitabine and Cedazuridine (Inqovi®) for Hematological Malignancies

Description: This PQI will discuss the rationale for the clinical use of the oral DNMT/CDA inhibitor decitabine/cedazuridine (DEC-C) for the management of intermediate-1, intermediate-2, and high-risk myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML).

Background: DEC-C is a fixed-dose combination of the hypomethylating agent decitabine and the cytidine deaminase inhibitor cedazuridine, which prevents degradation of decitabine in the gastrointestinal tract and liver, thus allowing for its oral dosing and absorption. The therapy was approved in July 2020.[1] It is indicated for the treatment of adult patients with MDS, including previously treated and untreated, de novo and secondary MDS with the following French American-British subtype (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and CMML) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups. It has long been noted that the development of an oral DNMT inhibitor would alleviate much of the burden associated with the treatment of MDS/CMML for those patients on IV DNMT inhibitors. Specifically, an oral option would decrease clinic visits, reduce travel time associated with treatment, reduce the need for IV access and the associated infection risks, and decrease exposure to health facilities. Published data of the phase 1/2 trials as well as preliminary data of the phase 3 trial demonstrates the safety and efficacy of the oral (PO) administration of DEC-C.[2,3,4] It is important to educate the providers in your practice on the rationale behind the approval of DEC-C using the following data from the phase 3 trial (ASCERTAIN study). In this study, presented at ASH 2019, intravenous (IV) decitabine was compared to PO decitabine/cedazuridine. 138 MDS intermediate, MDS high risk, and CMML patients were randomized 1:1 to one of two treatment arms - Sequence A (DEC-C 35 mg/100 mg daily x 5 days) in Cycle 1 followed by IV decitabine (20 mg/m^2 daily x 5 days) in Cycle 2, or Sequence B (IV decitabine 20 mg/m^2 daily x 5 days) in Cycle 1, followed by DEC-C (35 mg/100 mg daily x 5 days) in Cycle 2. All patients then received DEC-C on cycles 3 and onward. The study was conducted to demonstrate exposure bioequivalence between DEC-C and IV-DEC, comparing relevant pharmacokinetic (PK) and pharmacodynamic (PD) parameters, specifically the primary endpoint AUC equivalence over 5 days of dosing, and DNA methylation using the *LINE-1* assay, respectively. The 5-day oral:IV AUC ratio was 99%, demonstrating equivalent systemic exposure between the two formulations. The *LINE-1* assay demonstrated a difference of < 1% between the two formulations, which also confirmed the PK findings. The overall response rate from treatment was 65% (complete response + partial response + marrow CR + hematologic improvement), which is in line with what is seen with conventionally dosed IV decitabine. Transfusion independence was noted in 50% of patients in the phase 2 trial and 32.7% of patients in the phase 3 trial. There were no significant differences noted between the side effect profiles of the IV and PO formulations.

PQI Process:[1]

- Utilize the reporting tools available in the EMR to identify patients who are receiving IV decitabine for MDS or CMML and discuss the option of converting to oral DEC-C with their physician
- **Do NOT substitute DEC-C for an intravenous decitabine product within a cycle**
- Educate providers on the availability of decitabine to administer to patients as an alternative to traveling to the clinic for 5 consecutive days for IV infusion

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- Recommended dosage is 1 tablet (35 mg decitabine and 100 mg cedazuridine) PO once daily on Days 1 through 5 of each 28-day cycle (minimum 4 cycles) until disease progression/unacceptable toxicity
    - A complete or partial response may take longer than 4 cycles
- Obtain complete blood cell count and a comprehensive metabolic panel prior to initiating therapy and before each cycle
    - Delay the next cycle if absolute neutrophil count (ANC) ≤ 1,000/µL and platelets ≤ 50,000/µL in the absence of active disease
    - If hematologic recovery occurs (ANC ≥ 1,000/µL and platelets ≥ 50,000/µL) within 2 weeks of achieving remission, continue at the same dose
    - If hematologic recovery does not occur within 2 weeks of achieving remission:
        - Delay up to 2 additional weeks AND resume at a reduced dose by administering on Days 1 through 4; consider further dose reductions if myelosuppression persists
        - Maintain or increase dose in subsequent cycles as clinically indicated
        - Recommended dose reductions for myelosuppression:
            - First dose reduction: 1 tablet PO once daily on Days 1 through 4
            - Second dose reduction: 1 tablet PO once daily on Days 1 through 3
            - Third dose reduction: 1 tablet PO once daily on Days 1, 3 and 5
    - If serum bilirubin or AST/ALT ≥ 2x ULN: Delay next cycle and resume at same or reduced dose

Patient-Centered Activities:

- Provide an Oral Chemotherapy Education Sheet
- Consider providing Treatment Support Kit (TSK)
- Educate patient on schedule of administration: 5 consecutive days every 4 weeks (ex. Monday-Friday)
- Educate patient to not consume food 2 hours before and 2 hours after each dose
- Discuss with patient the risks of infection associated with bone marrow suppression and how to mitigate
- Educate the patient on when to contact the care team:
    - Fever of 100.4 degrees Fahrenheit (38 degrees Celsius)
    - Nausea/vomiting: educate on alternating different antinausea medication
    - Unusual bleeding
    - Bloody urine
    - Black/tarry stools
    - Painful mouth sores
- Discuss the management (using dietary/lifestyle/pharmacologic strategies) of constipation and diarrhea
- Monitor lab values before each cycle, focusing on neutropenia
- Educate to avoid taking over-the counter-medications that can thin the blood (ex. aspirin, NSAIDS)
- Patient Assistance: NCODA Financial Assistance Tool

References:

1. Inqovi® (decitabine and cedazuridine) [prescribing information]. Princeton, NJ: Taiho Oncology.
2. Savona, et al. An oral fixed-dose combination of decitabine and cedazuridine in myelodysplastic syndromes: a multicentre, open-label, dose-escalation, phase 1 study. Lancet Haematol 2019; 6: e194-203
3. Garcia-Manero, et al. Oral Cedazuridine/decitabine: a phase 2, pharmacokinetic/pharmacodynamic, randomized, crossover study in MDS and CMML. Blood April 2013. Epub ahead of print.
4. Garcia-Manero, et al. Pharmacokinetic Exposure Equivalence and Preliminary Efficacy and Safety from a Randomized Cross-Over Phase 3 Study (ASCERTAIN) of an Oral Hypomethylating Agent ASTX727 (cedazuridine/decitabine) Compared to IV Decitabine. 61st ASH Annual Meeting, Orlando, FL. 2019. Abstract #846.