Positive Quality Intervention: Obinutuzumab (Gazyva®) for Chronic Lymphocytic Leukemia and Follicular Lymphoma

Description: The purpose of this PQI is to provide an outline on obinutuzumab and to provide guidance on clinical considerations for its optimal medication management.

Background: Obinutuzumab is an intravenously administered monoclonal antibody targeted against CD-20. It is FDA approved for use in combination with chemotherapy and as monotherapy in chronic lymphocytic leukemia (CLL) and follicular lymphoma (FL). Infusion-related reactions are the most frequent and serious adverse effect, requiring premedication 30-60 minutes prior to administration along with rate titrations.\(^1\)

CLL: The CLL11 study compared chlorambucil monotherapy, obinutuzumab plus chlorambucil, and rituximab plus chlorambucil in previously untreated patients (median age 73) with CLL and no comorbidities. At median follow-up, progression-free survival (PFS) was statistically significantly higher in the obinutuzumab arm at 28.9 months compared to 15.7 months in the rituximab arm (p<0.0001). Overall survival and overall response rate were also reported to be statistically superior in the obinutuzumab arm (p-value not reported however), with similar rates of infusion reactions between both arms.\(^2\) Based on the results of this study along with others, obinutuzumab earned a recommendation in the first-line setting for elderly patients with CLL by NCCN.\(^3\)

FL: Similarly, the phase III GALLIUM study compared rituximab-based chemotherapy with obinutuzumab-based chemotherapy in newly diagnosed FL patients. At 3-year median follow-up, the obinutuzumab arm demonstrated a slightly higher PFS of 80% compared to the rituximab arm with 73.3% PFS (p=0.001). The study showed that obinutuzumab was associated with a greater incidence of Grade ≥ 3 infusion-related events (12.4% vs 6.7%; no p-value reported) and infections due to hematologic toxicities (20% vs 15.6%; no p-value reported).\(^4\) Based on these results, obinutuzumab in combination with chemotherapy is recommended in the first-line setting for FL by NCCN.\(^5\)

PQI Process: Upon order of obinutuzumab and prior to first and second infusion:

- Confirm correct patient, indication, dosing, and frequency

<table>
<thead>
<tr>
<th>Dosing</th>
<th>FL(^1)</th>
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<tbody>
<tr>
<td>Cycle 1: (Load dose)</td>
<td>Cycle 1: 1,000 mg IV on D1, D8, and D15; 28 day cycle</td>
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<td>D1 – 100 mg IV</td>
<td>Cycle 2-6*: in combination with bendamustine 1,000 mg IV on D1; 28 day cycle</td>
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<td>D2 – Give remaining 900 mg IV</td>
<td>Cycle 2-6/8***: in combination with CHOP (6 cycles) or CVP (8 cycles) 1,000 mg IV on D1; 21 day cycle</td>
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<td>D8 and D15 – 1,000 mg IV; 28 day cycle</td>
<td>Maintenance monotherapy: 1,000mg IV on D1; 2 month cycle for up to 2 years (start 2 months after previous dose)</td>
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<td>Cycle 2-6: 1,000 mg IV on D1; 28 day cycle</td>
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*Other off-label dosing/combinations exist including but not limited to: acalabrutinib, ibrutinib, venetoclax; note that cycle frequency may differ
** Relapsed FL or FL refractory to a rituximab-containing regimen, followed by obinutuzumab monotherapy
*** Indicated for previously untreated stage II bulky, stage III or IV follicular lymphoma (FL) followed by 2 additional obinutuzumab monotherapy cycles

- Ensure orders are placed for appropriate required premedications to prevent infusion reactions\(^1\)
  - **H\(_2\)-antagonist** (diphenhydramine 50 mg IV/PO) – administer at least 30 minutes prior\(^1\)
  - **Acutemaphen** 650-1000 mg PO – administer at least 30 minutes prior\(^1\)
  - **Corticosteroid** (dexamethasone 20 mg or methylprednisolone 80 mg IV) (hydrocortisone is not recommended as it has not been effective) – administer at least 60 minutes prior\(^1,3,5\)
  - Week 3: Provider may opt to omit premedications if no previous reactions\(^1\)

- Review vitals and laboratory values – at regular intervals with each dose and as clinically indicated\(^1,3,5\)

IMPORTANT NOTICE: NCODA has developed this Positive Quality Intervention platform. This platform is intended as an educational aid, does not provide individual medical advice, and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication. The materials contained in this platform do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA. NCODA does not ensure the accuracy of the information presented and assumes no liability relating to its accuracy. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional. It is the individual’s sole responsibility to seek guidance from a qualified healthcare professional. Updated 9.27.23
Monitor current CBC w/ diff, CMP
Electrolytes, phosphate, uric acid, LDH, renal function for tumor lysis syndrome (TLS)

- Screen for appropriate supportive therapies prior to first dose and ensure orders are placed
  - **Hepatitis B status**: review surface antigen/core antibody for prior infection/risk for reactivation
  - **TLS prophylaxis**: prophylactic hydration and antihyperuricemic (allopurinol) if high risk
  - **PJP pneumonia prophylaxis**: (sulfamethoxazole/trimethoprim)
  - **Antiemesis**: at least one medication for breakthrough emesis

- Address correct titration rate on orders based on dose number and infusion-related reactions:

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<th>CLL</th>
<th>FL</th>
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<td><strong>Week 1</strong></td>
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<td><strong>Day 1</strong>: 25 mg/hour over 4 hours. No titration.</td>
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<tr>
<td><strong>Day 2</strong>: If no infusion reactions with day 1: initiate rate at 50 mg/hour (25 mg/hour if infusion reaction occurred); may increase rate by 50 mg/hour every 30 minutes as tolerated to a MAX rate of 400 mg/hour</td>
<td>Initiate at 50 mg/hour; may increase by 50 mg/hour every 30 minutes as tolerated to a MAX rate of 400 mg/hour.</td>
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<td><strong>Week 2</strong>: If no infusion reactions, initiate at 100 mg/hour (50 mg/hour if infusion reaction occurred); may increase rate by 100 mg/hour every 30 minutes to a maximum rate of 400 mg/hour.</td>
<td>If no infusion reactions ≥ Grade 1 with dose 1: initiate rate at 100 mg/hour; may increase rate by 100 mg/hour every 30 minutes as tolerated to a MAX rate of 400 mg/hour. <strong>Optional</strong>: If no grade 3 infusion reactions, may utilize a 90 minute infusion: 100 mg/hour for 30 minutes; then infuse at 900 mg/hour for 60 minutes with continued premeds.</td>
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<td><strong>Week 3 and beyond</strong>: Initiate at 100 mg/hour; may increase rate by 100 mg/hour every 30 minutes to a maximum rate of 400 mg/hour.</td>
<td>See week 2 titration rates.</td>
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- Vials come in 1000 mg/40 mL intravenous solution which must be stored at 2-8°C and protected from light *Note: preparation of medication varies depending on indication and dose number
  - 100 mg doses in 100 mL NS; use immediately
  - 900 mg dose in 250 mL NS; may store at 2-8°C for up to 24 hours
  - 1,000 mg dose in 250 mL NS; may store at 2-8°C for up to 24 hours
  - Administer through a dedicated IV line (PVC or non-PVC administration set; do not mix with other medications; incompatible with dextrose or any diluents)

- Review concomitant treatment medications in regimen as necessary

**Patient-Centered Activities:**

- Provide printed and verbal education with calendar of treatment schedule and follow-up appointments
  - Cover common short and long-term adverse reactions
  - Advise that medication may cause hepatitis B reactivation
- Ensure prophylactic prescriptions (TLS, antiemetic, antibacterial, antiviral, antifungal) are picked up
- Emphasize signs/symptoms of infusion-related reactions with where to go and whom to call
- Neutropenic precautions due to potential bone marrow suppression and/ or infections

**References:**

1. Gazyva (obinutuzumab) [prescribing information].