Written By: Renee Shirakawa Kwock, PharmD, BCOP
USC Norris Comprehensive Cancer Center

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 $\geq$ 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

	CLL[1] (in combination with chlorambucil)*	**FL**[1]
Dosing	Cycle 1: (Load dose) D1 – 100 mg IV D2 – Give remaining 900 mg IV D8 and D15 – 1,000 mg IV; **28 day cycle**	Cycle 1: 1,000 mg IV on **D1, D8, and D15**; **28 day cycle**
		Cycle 2-6**: in combination with bendamustine 1,000 mg IV on D1; **28 day cycle**
	Cycle 2-6: 1,000 mg IV on D1; **28 day cycle**	Cycle 2-6/8***: in combination with CHOP (6 cycles) or CVP (8 cycles) 1,000 mg IV on D1; **21 day cycle**
		Maintenance monotherapy: 1,000mg IV on D1; **2 month cycle** for up to 2 years (start 2 months after previous dose)

*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_1-antagonist** (diphenhydramine 50 mg IV/PO) – administer at least 30 minutes prior[1]
  - **Acetaminophen** 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]

    - 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 [3,5,6]
    - **Hepatitis B status**: review surface antigen/core antibody for prior infection/risk for reactivation
    - **TLS prophylaxis**: prophylactic hydration and antihyperuricemic (allopurinol) if high risk[1]
    - **PJP pneumonia prophylaxis:** (sulfamethoxazole/trimethoprim)[6]
    - **Antiemesis**: at least one medication for breakthrough emesis[7]
- Address correct titration rate on orders based on dose number and infusion-related reactions:[1]

	CLL[1]	**FL**[1]
Week 1	**Day 1**: 25 mg/hour over 4 hours. No titration. **Day 2**: 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	Initiate at 50 mg/hour; may increase by 50 mg/hour every 30 minutes as tolerated to a MAX rate of 400 mg/hour.
Week 2	If no infusion reactions, initiate at 100mg/hour (50 mg/hour if infusion reaction occurred); may increase rate by 100 mg/hour every 30minutes to a maximum rate of 400 mg/hour.	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. **Optional**: 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.
Week 3 and beyond	Initiate at 100 mg/hour; may increase rate by 100 mg/hour every 30 minutes to a maximum rate of 400 mg/hour.	See week 2 titration rates.

- 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)[1]
- 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[1]
- 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].
2. Goede, V., et al. (2014). Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *The New England journal of medicine*, *370*(12), 1101–1110.
3. National Comprehensive Cancer Network. *Chronic lymphocytic leukemia/small lymphocytic lymphoma* [PDF]. NCCN.
4. Marcus, R., et al. (2017). Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. *The New England journal of medicine*, *377*(14), 1331–1344.
5. National Comprehensive Cancer Network. *B-Cell Lymphomas* [PDF]. NCCN.
6. National Comprehensive Cancer Network. *Prevention and Treatment of Cancer-Related Infections* [PDF]. NCCN.
7. National Comprehensive Cancer Network. *Antiemesis* [PDF]. NCCN.