Managing Infusion-Related Reactions for Patients With Chronic Lymphocytic Leukemia Receiving Obinutuzumab

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Background: In patients with previously untreated chronic lymphocytic leukemia (CLL) and comorbitides, treatment with the glycoengineered, type II anti-CD20 monoclonal antibody obinutuzumab (Gazyva®) (GA101) plus chlorambucil (Leukeran®) was associated with superior outcomes to rituximab (Rituxan®) plus chlorambucil, with a similar safety profile. However, a higher occurrence of infusion-related reactions (IRRs) was reported with obinutuzumab. These reactions typically require additional management.

Objectives: The focus of this article is to provide oncology nurses and physicians with advice for obinutuzumab IRR management based on clinical trial data and nursing experience.

Methods: The authors reviewed the published management strategies for IRRs with obinutuzumab that were identified during the phase III CLL11 trial and an expanded access phase IIb study (ML28979). Practical advice for obinutuzumab IRR management was developed based on available clinical trial information and nursing experience.

Findings: IRRs with obinutuzumab are generally manageable. Most IRRs (all grades), and all grade 3–4 IRRs, occurred during the first infusion. Therefore, IRR management could be improved substantially with extra vigilance at this early stage.

Treatment regimens containing the anti-CD20 monoclonal antibody rituximab (Rituxan®) have improved clinical outcomes in chronic lymphocytic leukemia (CLL) versus chemotherapy alone (Byrd et al., 2005; Foà et al., 2014; Goede et al., 2014; Hallek et al., 2010; Hillmen et al., 2014; Tam et al., 2008). Consequently, rituximab plus chlorambucil (Leukeran®) (R-Clb) is a current standard-of-care regimen for treatment-naïve, comorbid CLL (Hagemeister, 2010; Keating, 2010). However, CLL remains incurable using standard approaches (Rioufol & Salles, 2014); therefore, new therapies are needed to prolong CLL remission.

Obinutuzumab (Gazyva®) (GA101) is a novel, humanized, anti-CD20 monoclonal antibody (Abraham & Stegner, 2014) approved by the U.S. Food and Drug Administration in November 2013 for use with Clb regimens in patients with treatment-naïve CLL (Lee et al., 2014). The glycoengineered, type II antibody obinutuzumab enhances induction of antibody-dependent, cell-mediated cytotoxicity and direct cell death when compared to the type I antibody rituximab (Glennie, French, Cragg, & Taylor, 2007; Morschhauser et al., 2009, 2010; Mössner et al., 2010; Niederfellner et al., 2011). Obinutuzumab plus chlorambucil (G-Clb) has increased
TABLE 1. National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 for Infusion-Related Reactions by Grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
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<tbody>
<tr>
<td>1</td>
<td>Mild, transient reaction; interruption/intervention not indicated</td>
</tr>
<tr>
<td>2</td>
<td>Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, IV fluids); prophylactic medications indicated 24 hours or less</td>
</tr>
<tr>
<td>3</td>
<td>Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion), recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>


progression-free survival (PFS) when compared to R-Clb in treatment-naive, comorbid CLL (Goede et al., 2014). Obinutuzumab is formulated as a sterile, clear, colorless to slightly brown, preservative-free liquid at a concentration of 25 mg/ml for IV administration, supplied in a 1,000 mg single-use vial (Genentech, Inc., 2014b).

Many IV cancer therapies, including monoclonal antibodies, are associated with infusion-related reactions (IRRs), which are adverse reactions to the infusion of pharmacologic/biologic substances (Jung, Kang, Lee, & Cho, 2014; Vogel, 2010). IRRs range from grade 1–2 events (mild and transient reactions that do not require intervention or respond promptly to symptomatic treatment) to grade 3–4 events (reactions that may be life threatening and may require hospitalization for prolonged clinical sequelae) (National Cancer Institute, 2010) (see Table 1). Monoclonal antibodies, such as obinutuzumab, can induce B-cell lysis, predisposing patients to high cytokine release associated with tumor destruction and an increased incidence of IRRs (Vogel, 2010).

Obinutuzumab IRRs are treatment-related adverse events (AEs) typically requiring additional management (Goede et al., 2014). Because most obinutuzumab IRRs occur during the first infusion (Goede et al., 2014), the key clinical aim should be to support patients through an IRR to ensure that they can complete the treatment course and achieve maximal clinical benefit. Supporting oncology nurses and physicians in implementing effective IRR management strategies and enhancing their understanding of which patients may have an increased risk of developing IRRs will maximize the clinical benefit for patients and minimize adverse sequelae.

The objectives of this article are to provide oncology nurses and physicians with an overview of the clinical and safety profiles of obinutuzumab and to discuss real-world IRR management experiences and published IRR management strategies.

Infusion-Related Reaction Occurrences

The mechanisms of IRRs remain unclear. Because IRRs are multifactorial events, some identified factors associated with IRRs can be influenced, whereas others cannot (Vogel, 2010). Obinutuzumab-related factors associated with IRRs that can be influenced (and, therefore, improved) include staff education regarding the safety profile of obinutuzumab (including IRR management), infusion speed and dose, premedication, and concomitant medication. Factors that cannot be influenced include release of vasoactive/inflammatory mediators by anti-CD20–targeted B cells, effector cell activation, preexisting immunoglobulin E–mediated immunity, comorbidities, genetic predisposition to IRR development, and baseline lymphocyte counts/tumor burden (Goede et al., 2014).

TABLE 2. Grade 3 or Higher Adverse Events With an Incidence of 3% or Higher in the Safety Population of the CLL11 Study

<table>
<thead>
<tr>
<th>Event</th>
<th>G-Clb Versus Clb</th>
<th>R-Clb Versus Clb</th>
<th>G-Clb Versus R-Clb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
</tr>
<tr>
<td>Infusion-related</td>
<td>51 21 – –</td>
<td>9 4 – –</td>
<td>67 20 12 4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>84 35 18 16</td>
<td>60 27 18 16</td>
<td>111 33 91 28</td>
</tr>
<tr>
<td>Anemia</td>
<td>11 5 5 4</td>
<td>10 4 5 4</td>
<td>14 4 12 4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>27 11 5 4</td>
<td>8 4 5 4</td>
<td>35 10 10 3</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>13 5 – – –</td>
<td>3 1 – –</td>
<td>15 4 3 1</td>
</tr>
<tr>
<td>Infections</td>
<td>27 11 16 14</td>
<td>30 13 16 14</td>
<td>40 12 44 14</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8 3 4 3</td>
<td>11 5 4 3</td>
<td>13 4 17 5</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4 2 5 4</td>
<td>4 2 5 4</td>
<td>8 2 4 1</td>
</tr>
</tbody>
</table>

*The safety population included all patients who received at least one dose of study medication. Shown are adverse events of grade 3, 4, or 5 with an incidence of 3% or higher in any treatment group, irrespective of whether the event was considered related or unrelated to treatment by the investigators.

Clb—chlorambucil; G—obinutuzumab plus chlorambucil; R—rituximab plus chlorambucil

IRRs have a variety of symptoms that occur within 24 hours of an infusion and often start during administration (Vogel, 2010). For example, patients experiencing mild or moderate obinutuzumab IRRs may have symptoms such as fever, chills, nausea, vomiting, hypotension, fatigue, hypoxia, and dyspnea (Cartron et al., 2014). Obinutuzumab IRRs typically occur during the first hour or shortly after the first infusion, and the incidence and severity decreases with subsequent infusions (F. Hoffmann-La Roche Ltd., data on file, 2014).

The rates of obinutuzumab IRRs (69% [grade 3 or greater, 21%]) (Genentech, Inc., 2014b) are higher than the occurrence of hypersensitivity/allergic reactions with standard chemotherapy agents for CLL, such as bendamustine (Treanda®) (5%–8% [grade 3 or greater, 1%]), Clb (1%–3% [grade 3 or greater, 0%]), and fludarabine (Fludara®) (grade 3 or greater, 2%) (Flinn et al., 2007; Friedberg et al., 2008; Hillmen et al., 2007; Knauf et al., 2009). Among monoclonal antibody therapies, all-grade IRR rates with obinutuzumab (69%) are similar to alemtuzumab (Campath®) (14% to ≥ 64%) and rituximab (77%); grade 3 or greater IRR rates with obinutuzumab (21%) are similar to alemtuzumab (10%–35%) but higher than rituximab (10%) (Elter et al., 2011; Genentech, Inc., 2014b, 2014d; Genzyme Corporation, 2014; Hillmen et al., 2007). Lower IRR rates are reported for other monoclonal antibodies (Amgen, Inc., 2014; Bristol-Myers Squibb Company, 2013; Chung, 2008; Genentech, Inc., 2014a, 2014c; Plosker & Figgitt, 2003). IRR rates with monoclonal antibodies are similar to those reported for taxanes (20%–41% [grade 3 or greater, 2%–10%]) (Bristol-Myers Squibb Company, 2011; Sanofi-Aventis, 2013) and platinum agents (2%–16% [grade 3 or greater, 1%–4%]) (Brandi et al., 2003; Bristol-Myers Squibb Company, 2004; Chung, 2008; Markman et al., 1999; Polyzos et al., 2001; Saif, 2006; Siu, Chan, & Au, 2006; Teva Pharmaceuticals, 2012). Similar to monoclonal antibodies, most taxane IRRs occur during the first infusion, whereas reactions to platinum agents typically occur after six or more infusions. However, the different reaction classifications (IRR, hypersensitivity, allergic reaction) cannot be compared directly because the grading criteria used to assess these reactions are likely to vary between agents. In addition, hypersensitivity reactions are typically immunoglobulin E-mediated, whereas IRRs are not, and hypersensitivity reactions typically worsen with subsequent doses while IRRs improve. Also, IRR incidence is likely to vary between different oncology diagnoses.

Obinutuzumab Efficacy

The phase III CLL11 trial compared G-Clb, R-Clb, and Clb alone in previously untreated, comorbid CLL (Goede et al., 2014). In stage 1, patients were randomized 2:2:1 to receive G-Clb, R-Clb, or Clb. A significant prolongation of investigator-assessed median PFS was observed with G-Clb versus Clb (26.7 versus 11.1 months, p < 0.001), with a hazard ratio (HR) of 0.18 (95% confidence interval [CI] [0.13, 0.24]), demonstrating an 82% reduction in the risk of CLL progression, relapse, or death. Median PFS was also improved with R-Clb versus Clb (16.3 versus 11.1 months, HR = 0.44, 95% CI [0.34, 0.57], p < 0.001). In stage 2, the Clb group was closed and the patients were randomized 1:1 to the R-Clb or G-Clb arm. Stage 2 data (median observation time: 23 months) demonstrated a significant and clinically

<table>
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<th>TABLE 3. Obinutuzumab (Gazyva®) Dosing Schedule</th>
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<tbody>
<tr>
<td>Cycle</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>8, 15</td>
</tr>
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<td>2–6</td>
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*In the absence of infusion-related reactions/hypersensitivity during previous infusions.


<table>
<thead>
<tr>
<th>TABLE 4. Management of Infusion-Related Symptoms When Receiving Obinutuzumab (Gazyva®) by Grade</th>
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<tbody>
<tr>
<td>Grade*</td>
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<tr>
<td>-------</td>
</tr>
<tr>
<td>1–2</td>
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<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

*Refer to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, for the grading of symptoms (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf)

Patient should be treated with acetaminophen and an antihistamine such as diphenhydramine, if they have not received these within the previous four hours. IV saline may be indicated. For bronchospasm, urticaria, or dyspnea, patients may require antihistamines, oxygen, corticosteroids (e.g., 100 mg IV prednisolone or equivalent), and/or bronchodilators. For hypotension, patients may require vasopressors. Upon complete resolution of symptoms, the infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion may be escalated in increments of 50 mg per hour every 30 minutes to a maximum rate of 400 mg per hour. Note. From “Gazyva® (obinutuzumab),” by Genentech, Inc., 2016. Retrieved from http://www.gazyva.com/hcp/dosing-administration/infusion-reactions. Copyright 2016 by Genentech, Inc. Reprinted with permission.
meaningful improvement in median PFS for G-Clb versus R-Clb (26.7 versus 15.2 months, HR = 0.39, 95% CI [0.31, 0.49], p < 0.001). Overall survival (OS) was improved with G-Clb versus Clb (HR = 0.41, 95% CI [0.23, 0.74], p = 0.002); no significant differences were observed for R-Clb versus Clb or G-Clb versus R-Clb. OS was a secondary endpoint, and the follow-up period was short. OS medians were not reached (Goede et al., 2014).

Clb was well-tolerated for CLL treatment in older adult patients unable to tolerate fludarabine (Eichhorst et al., 2009; Goede et al., 2014). The CLL11 Clb dose and dosing schedule were based on the CLL5 trial. In CLL5, older adult patients with CLL treated with Clb had similar PFS and OS to patients who received fludarabine, with significantly lower hematologic toxicity (Eichhorst et al., 2009). The median dose of Clb in CLL5 was 0.5 mg/kg twice monthly, and the median treatment duration was 6.5 months. The dose and duration of Clb in CLL11 (0.5 mg/kg twice monthly, six-monthly cycles) were chosen with the intention of adequately treating, but not overtreating, this patient population (Goede et al., 2014). As all treatment arms in CLL11 used the same Clb dose, significant differences in PFS between Clb and combination arms were attributed to the antibody rather than lower Clb dosing.

Obinutuzumab Safety

In CLL11, G-Clb had a similar safety profile to R-Clb. However, higher incidences of thrombocytopenia and IRRs were noted with G-Clb versus R-Clb (Goede et al., 2014) (see Table 2). Obinutuzumab-related IRRs occurred primarily during the first infusion, with about 70% of IRRs starting within two hours of beginning the first infusion (F. Hoffmann-La Roche Ltd., data on file, 2014). After the first obinutuzumab 1,000 mg dose, all-grade IRRs were infrequent, and no grade 3–4 IRRs were reported and similar trends have been observed with rituximab. No IRR-related deaths occurred during CLL11. More patients who received G-Clb than R-Clb experienced IRRs leading to treatment discontinuation (7% versus less than 1%), hospitalization (8% versus 2%), and treatment interruption or delay (36% versus 21%) (Goede et al., 2014). Overall, 7% of the G-Clb arm discontinued because of a grade 3–4 IRR, and treatment was not restarted for any of those patients (F. Hoffmann-La Roche Ltd., data on file, 2014).

An expanded access, U.S.-based, open-label, phase IIb study (ML28979) further evaluated G-Clb safety in treatment-naive CLL requiring treatment (F. Hoffmann-La Roche Ltd., data on file, 2014). Obinutuzumab 1,000 mg IV was administered for as many as six cycles (28-day cycles). For cycle (C)1, the initial dose was split across two days (100 mg day 1; 900 mg day 2). Clb 0.5 mg/kg was administered orally on D1 and D15, C1–C6. Nineteen patients received one or more dose of G-Clb (safety-evaluable population). The overall safety profile in ML28979 was consistent with that in CLL11 (Goede et al., 2014). The most commonly reported treatment-emergent AE was IRR (13 patients, 68%); of the 18 IRRs reported, only one was grade 3 or greater. The most frequent symptoms experienced within 24 hours of an infusion were nausea (47%), flushing (37%), dyspnea and vomiting/other (26%), and chills (16%). Most IRRs (17 of 18, 94%) occurred during C1, predominantly on D1 (13 IRRs on D1, four on D2, and one on D1, C2).

Clinical Trial Experience in the Management of Infusion-Related Reactions

Appropriate IRR management remains important so that patients with CLL can receive full doses of chemotherapy and maximize clinical benefits. The obinutuzumab dosing schedule for CLL (100 mg on D1 and 900 mg on D2 of C1, 1,000 mg on D8 and D15 of C1, and 1,000 mg on D1 of C2–C6) was calculated based on pharmacokinetic modeling and then confirmed in phase I/II studies in CLL and non-Hodgkin lymphoma (NHL) (Cartron et al., 2014; Morschhauser et al., 2013; Radford et al., 2013; Salles et al., 2012, 2013; Sehn et al., 2012). In part two of the phase I/II GAUGUIN trial, obinutuzumab 1,600/800 mg demonstrated an improvement in efficacy versus 400/400
mg in NHL (first dose D1, D15, C1; second dose D1, C2–C6) (Morschhauser et al., 2013; Salles et al., 2013). Additional pharmacokinetic modeling and simulation indicated that a 1,000 mg fixed-dose regimen with an additional infusion on D8 of C1 would provide equivalent exposure to the 1,600/800 mg regimen but with increased convenience (Morschhauser, Salles, & Cartron, 2011). The 1,000 mg regimen was integrated into the GAUGUIN study in CLL, with an additional dose on D15 of C1 (Cartron et al., 2014), and was taken forward for use in CLL11 (Goede et al., 2014). Pharmacokinetic modeling of early CLL11 data indicated that a strong clinical response would be achieved with the 1,000 mg regimen, and this was confirmed in clinical data from CLL11 (Gibiansky et al., 2014). The obinutuzumab 1,000 mg regimen was established in the ML28979 study (F. Hoffmann-La Roche Ltd., data on file, 2014) (see Table 3).

Splitting the first dose of obinutuzumab over two days in C1 (to reduce the risk of IRRs) became mandatory following the results of CLL11 (100 mg D1, 900 mg D2). Clb 0.5 mg/kg was administered orally on D1 and D15 of C1–C6. ML28979 included additional safety measures (including premedication to reduce the risk of IRRs, and adjusting infusion rate in response to infusion reaction symptoms) that were implemented in CLL11 over time. These adjustments in ML28979 (n = 19) have resulted in only one grade 3 or greater IRR being reported with obinutuzumab.

Premedication was recommended to reduce the risk of IRRs. For example, for C1, D1, and D2, all patients required premedication with an IV glucocorticoid administered at least one hour prior to the infusion, oral acetaminophen (1,000 mg), and an antihistamine, such as diphenhydramine (Benadryl®) (50 mg), administered at least 30 minutes before starting each infusion. Dexamethasone (Decadron®) (20 mg) or methylprednisolone (Medrol®) (80 mg) were the most suitable glucocorticoids to use, as hydrocortisone has not been shown to be effective in reducing rates of IRRs. Obinutuzumab was given as a slow IV infusion through a dedicated line, and IV infusion pumps were used to control the infusion rate. After the end of the first infusion, the IV line remained in place for about two hours to allow administration of IV drugs, if necessary. If no AEs occurred after two hours, the IV line was removed. For subsequent infusions, the IV line remained in place for about one hour from the end of the infusion, and was removed if no AEs occurred after one hour. If a patient experienced any grade of IRR, the infusion was adjusted, as shown in Table 4 (F. Hoffmann-La Roche Ltd., data on file, 2014).

During CLL11, healthcare professionals ascertained how best to manage or minimize the risk of IRRs, and several protocol amendments were made as the study progressed. Originally, administration of obinutuzumab 1,000 mg IV was on D1, D8, and D15, C1 and D1, C2–C6 (based on previous pharmacokinetic knowledge) (Goede et al., 2014; Morschhauser et al., 2011). The protocol was amended on four occasions during the study: patients with lymphocytes greater than 25 x 10^9/L received corticosteroid premedication, corticosteroid premedication was recommended for all patients, antihypertensive drugs prior to the initial obinutuzumab dose were stopped, and a slow infusion rate and mandatory splitting of the first dose were introduced. (Hypotension may occur during obinutuzumab IV infusions. Consider withholding anti-hypertensive treatments for 12 hours prior to and throughout each obinutuzumab infusion, and for the first hour after administration.) These protocol amendments reduced the rate of hypertensive AEs due to obinutuzumab infusion.

**Background information**

- Male, aged 82 years
- Binet stage C disease
- White blood cell count: 22.9 x 10^9/L
- Absolute lymphocyte count: 22.44 x 10^9/L
- Neutrophil count: 0.27 x 10^9/L
- Hemoglobin: 8.2 g/dL
- Cytogenetics: uncharacterized IgHV translocation; p53; and intact t(X:14)(p11;q32)
- Coexisting medical conditions: CIRS score of 2, low CCR (54.8 ml per minute); BCC treated with RT; torn retina in left eye; and bowel cancer (Dukes’ A) in remission

**IRR management strategy**

- Patient was provided with information on IRRs before the infusion.
- Patient was premedicated with paracetamol, antihistamine, and 20 mg IV dexamethasone (one hour before the infusion).
- Second cannula was inserted into patient’s other arm to allow rapid emergency drug administration.
- Infusion was stopped when IRRs occurred (grade 2–3); symptoms were treated.
- Infusion was restarted at either the lowest or previously tolerated rate once IRRs resolved; blood pressure was monitored.
- Infusion was stopped because of an IRR (grade 2); symptoms were treated.
- When symptoms resolved, the infusion was restarted at the faster rate.
- Infusion was successfully completed.
- By current recommendations, the patient would have qualified to receive the next whole 1,000 mg dose in one day, if time allowed.

**FIGURE 2. Management Strategies Employed for Infusion-Related Reactions With Obinutuzumab (Gazyva®) on Cycle 1, Day 2: Case Study B**
all-grade IRRs from 88% (before any protocol amendments) to 55% (after all protocol amendments), but the rate of grade 3–4 IRRs (17%) did not change (Goede et al., 2014). However, some of the patient groups in the analysis were too small to draw conclusions. For example, although the final patient group (for whom all of the measures were in place) experienced the lowest rate of all-grade IRRs and relatively low rates of grade 3–4 and serious IRRs, rates were not conclusively improved versus the previous groups. As such, the combination of all measures, including the dose splitting between D1 and D2, are considered the current best practice for administering obinutuzumab (F. Hoffmann-La Roche Ltd., data on file, 2014).

Management of Infusion-Related Reactions With Obinutuzumab

In the United States, alongside the obinutuzumab launch at new sites, the Nurse Educational Program provides training on obinutuzumab administration and monitoring on IRR management for oncology nurses. Examples of how obinutuzumab IRRs have been successfully managed are shown in case studies (see Figures 1 and 2).

Preparation
- Reassure and prepare patients for the possibility of IRRs and suggest they wear comfortable clothing.
- Ensure the patient is adequately hydrated; recommend that he or she drinks plenty of water in the two days before the infusion.
- Ensure the patient avoids the use of antihypertensive medications for the 12-hour period before the infusion and throughout each infusion. Hypotension may occur during obinutuzumab (Gazyva®) IV infusions. Consider withholding antihypertensive treatments for 12 hours prior to and throughout each obinutuzumab infusion, and for the first hour after administration.

Before and during the infusion
- Premedicate the patient with a corticosteroid and an antihistamine/anti-pyretic.
- Insert a second cannula in the patient’s other arm before the infusion to enable easy administration of drugs to treat any IRRs that may occur.
- Prime the IV equipment with obinutuzumab, not saline, to enable the actual entry time to be recorded.
  - Alternatively, consider that obinutuzumab entry into the patient may have been delayed before increasing the infusion rate.
- Administer the first 100 mg at a rate of 25 mg per hour for four hours, with the remaining 900 mg given the next day.
- Ensure constant close supervision of the patient, particularly monitoring vital signs at regular intervals during first infusion and the first two hours of dosing for subsequent infusions, and performing ongoing assessment for IRRs.

Discontinuation
- Obinutuzumab should be permanently discontinued if a grade 4 IRR occurs, or if more than one grade 3 reaction occurs during a single infusion.

Based on real-world nursing experience of obinutuzumab administration, a checklist has been produced of precautions to be taken before and during infusion aimed at reducing the chance of IRRs and to assist in managing patients who experience reactions (see Figure 3). Obinutuzumab should only be administered by oncology nurses with knowledge to assess and manage severe IRRs that can be fatal if they occur. Of note, prior to each infusion, all patients should receive premedication to reduce the risk of IRRs; the initial dose of obinutuzumab should be given at a slow infusion rate, with a split dose over two days (100 mg D1, 900 mg D2 on C1); patients should be monitored for IRR symptoms, such as fever, chills, nausea, vomiting, hypotension, fatigue, hypoxia, and dyspnea (Cartron et al., 2014; Genentech, Inc., 2014b); if no IRR or hypersensitivity is observed, the rate of infusion can be increased accordingly.

Administration in countries other than the United States may differ from what is discussed in this article. It may be possible in some countries to complete both infusions on D1 if no IRRs have occurred during the first 100 mg infusion (total of eight hours or more required).

Conclusion

Many IV cancer therapies, including monoclonal antibodies, are associated with IRRs. In comorbid CLL, G-Clb provides significant prolongation in PFS versus R-Clb, with a similar safety profile. Obinutuzumab has an increased incidence of IRRs versus rituximab, but these IRRs are generally manageable. No fatal obinutuzumab IRRs have been reported, and most patients are able to complete the full treatment course. With effective management, IRR rates can potentially be substantially reduced. Most obinutuzumab IRRs occur during the first 1,000 mg administered dose (D1 and D2) and all grade 3–4 IRRs seem to occur during this early stage. Therefore, IRR management could be improved substantially with premedication and extra vigilance (in particular, monitoring vital signs during first infusion and assessment for IRRs) during the first infusion. IRRs are typically mild or moderate and can be managed by premedication or slowing or temporarily stopping the infusion. Premedication before each infusion, splitting the first dose over two days (100 mg D1, 900 mg D2), and a slow infusion rate appear to help mitigate possible IRRs. The incidence of IRRs decreases with subsequent infusions. Appropriate IRR management is important so that patients can receive the potential benefit from the chemotherapy while minimizing AEs.
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