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Inotuzumab Ozogamicin in Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

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Abstract

Despite initial complete remission rates of up to 90%, long-term, disease-free survival remains poor in patients with newly diagnosed acute lymphoblastic leukemia (ALL). Response to salvage chemotherapy is suboptimal; therefore, novel therapeutic agents are being investigated in order to improve outcomes in these patients. Inotuzumab ozogamicin is a CD22-directed antibody-drug conjugate recently approved by the US Food and Drug Administration for the treatment of adults with relapsed or refractory B-cell precursor ALL. Inotuzumab ozogamicin improves response rate, minimal residual disease negativity, and survival compared to standard chemotherapy in this population. In addition, it offers more opportunities to proceed to an allogeneic stem cell transplant in patients who otherwise may not be candidates.

Acute lymphoblastic leukemia (ALL) accounts for approximately 20% of all adult leukemias, with an estimated 5,960 new cases and 1,470 deaths in the United States in 2018 (Siegel, Miller, & Jemal, 2018). Currently, available induction therapy for adults with newly diagnosed disease results in complete remission (CR) rates of 60% to 90% (Bassan & Hoelzer, 2011; Faderl et al., 2010). Despite initial CR rates, long-term disease-free survival is 35% (Bassan & Hoelzer, 2011).

Response to salvage chemotherapy depends on disease and patient characteristics (Kantarjian et al., 2010). In adults experiencing first relapse, a second CR is achieved in up to 45% of patients, with a median survival of 5 to 9 months (Tavernier et al., 2007; Topp, Gockbuget, Stein, 2015). Adults who relapse within 12 months after first CR are refractory to front-line chemotherapy or after failing multiple lines of therapy have a CR rate of about 20% to 30% and a median survival of 3 to 6 months (Fielding et al., 2007; Kantarjian et

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al., 2010; O'Brien et al., 2008). Due to the poor outcomes associated with salvage chemotherapy in adults with relapsed or refractory ALL, investigation of novel treatment strategies is warranted.

CD22 is a cell-surface glycoprotein that is found in more than 90% of patients with pre-B ALL and mature B-cell ALL (George, Kantarjian, Jabbour, & Jain, 2016). It has emerged as an attractive target for B-cell cancers due to the lack of expression on normal tissues and hematopoietic stem cells. In addition, it is not shed into the extracellular matrix (George et al., 2016; Kantarjian et al., 2016). Inotuzumab ozogamicin (Besponsa), a recently US Food and Drug Administration (FDA)–approved CD22-targeted therapy, is the focus of this article.

MECHANISM OF ACTION

Inotuzumab ozogamicin is a humanized CD22-directed antibody-drug conjugate (ADC). Inotuzumab ozogamicin consists of a CD22 antibody conjugated to calicheamicin, a natural product derived from *Micromonospora echinospora*, via an acid-hydrolyzable butanoic acid linker. Once bound to CD22-expressing tumor cells, it is internalized and delivers the cytotoxic calicheamicin via hydrolytic cleavage of the linker. Once released, calicheamicin binds to the minor groove of DNA leading to double-strand DNA breaks, subsequently inducing cell-cycle arrest and apoptosis. The ADC ensures effect on CD22-expressing tumor cells rather than normal cells, thus reducing toxicity (DiJoseph et al., 2004; Kantarjian et al., 2016; Kantarjian, Thomas, Wayne, & O'Brien, 2012; Shor, Gerber, & Sapra, 2015). Calicheamicin is nonenzymatically metabolized and is approximately 97% protein bound. The half-life of elimination of inotuzumab ozogamicin is 12.3 days (Pfizer, 2017).

CLINICAL TRIALS

A phase II trial in relapsed or refractory pre-B ALL conducted by Kantarjian and colleagues (2013) studied inotuzumab ozogamicin single dose (1.3 to 1.8 mg/m^2 every 3 to 4 weeks) and weekly dose schedules (0.8 mg/m^2 on day 1, 0.5 mg/m^2 on day 8, 15 every 3 to 4 weeks). The median age was 39.5 years old and most patients received prior salvage treatments, with 38% of patients receiving inotuzumab ozogamicin as second salvage therapy and 30% as third salvage therapy or beyond. The response rate, including CR, CR with incomplete platelet recovery (CRp), and CR with incomplete hematologic recovery (CRi), was 58%. The CR rate was 19% and did not differ between the single dose and weekly schedule (18% vs. 20%, respectively). The median overall survival (OS) was 6.2 months and median remission duration was 7 months. The minimal residual disease (MRD) status did not impact median survival (7.9 months in MRD-negative patients vs. 7.8 months in MRD-positive patients, $p = .48$). More patients who received inotuzumab ozogamicin single dose proceeded to a hematopoietic stem cell transplant (HSCT) compared to the weekly schedule (45% vs. 34%, respectively). However, more adverse events, especially liver toxicities, were observed with the single-dose schedule. Veno-occlusive disease (VOD) was observed after HSCT in 1 of 14 (7.1%) patients on a weekly dosing schedule compared with 5 of 22 (22.7%) patients on single dose (Kantarjian et al., 2013).

Kantarjian and colleagues (2016) conducted an open-label, multicenter, phase III trial to determine the efficacy and safety of inotuzumab ozogamicin compared with standard intensive chemotherapy. The trial included 326 adults with relapsed or refractory, CD22-positive, Philadelphia chromosome (Ph)–positive or Ph-negative B-cell ALL due to receive the first or second salvage therapy. Patients with Ph-positive disease were required to have failed treatment with at least one second-generation tyrosine kinase inhibitor (TKI). Patients were randomized to receive inotuzumab ozogamicin (N = 164) or investigator's choice of chemotherapy (N = 162). The primary endpoints were CR (including CRi) and OS. Secondary endpoints evaluated were safety, duration of remission, progression-free survival (PFS), subsequent HSCT, and MRD status in patients achieving CR (Kantarjian et al., 2016).

The initial 218 patients (109 in each group) randomized were included in the analysis of CR. Treatment with inotuzumab ozogamicin compared with standard chemotherapy resulted in a significantly higher CR (80.7% vs. 29.4%, $p < .001$) and MRD negativity (78.4% vs. 28.1%, $p < .001$). Significantly higher CR was seen in patients with less than 90% CD22 expression (79.2% vs. 25%,

$p < .001$) and greater than or equal to 90% CD22 expression (CR 82.4% vs. 36.5%, $p < .001$) when compared with standard chemotherapy. The median duration of remission was 4.6 months with inotuzumab ozogamicin compared with 3.1 months with standard chemotherapy ($p = .03$). Following inotuzumab ozogamicin, significantly more patients proceeded to HSCT compared with standard chemotherapy (41% vs. 11%, $p < .001$). In the survival analysis that included all 326 randomized patients, PFS (5.0 months vs. 1.8 months, $p < .001$) was significantly longer with inotuzumab ozogamicin. The second primary objective of OS, although longer (7.7 months with inotuzumab ozogamicin vs. 6.7 months with standard chemotherapy, $p = .04$), did not meet the prespecified significance level of .0208 (significance level adjusted for the two prespecified interim analyses). However, this data violated the proportional hazards assumption and an exploratory post hoc analysis was conducted. This analysis showed a significantly longer OS (13.9 months vs. 9.9 months, $p = .005$) with inotuzumab ozogamicin compared with standard chemotherapy (Kantarjian et al., 2017). Based on these results, inotuzumab ozogamicin was FDA approved on August 17, 2017, for the treatment of adults with relapsed or refractory B-cell precursor ALL (Pfizer, 2017).

ADVERSE EFFECTS

Table 1 lists the common adverse reactions (≥ 20%) associated with inotuzumab ozogamicin and standard chemotherapy as reported in the phase III trial (Kantarjian et al., 2016). The most common hematologic toxicity was cytopenias in both inotuzumab ozogamicin and standard therapy groups. However, the occurrence of greater than or equal to grade 3 thrombocytopenia and febrile neutropenia was lower with inotuzumab ozogamicin than with standard therapy (Kantarjian et al., 2016; Pfizer, 2017).

Inotuzumab ozogamicin has a black box warning for hepatoxicity, including VOD and increased risk of post-HSCT, non-relapse mortality (Pfizer, 2017). Veno-occlusive disease associated with inotuzumab ozogamicin is thought to be related to calicheamicin-induced cytotoxicity to hepatic sinusoidal endothelial cells (Godwin, Gale, & Walter, 2017; Guffroy et al., 2017). In the phase III trial, VOD occurred more commonly with inotuzumab ozogamicin compared with standard intensive chemotherapy (11% vs. 1%). Veno-occlusive disease occurred in five patients during or shortly after inotuzumab ozogamicin treatment, two of which received HSCT prior to the trial. Of the 48 patients who proceeded to HSCT after receiving inotuzumab ozogamicin, VOD was reported in 10 patients, 3 of which received HSCT prior to the trial. Seven of 10 patients who devel-

Table 1. Common Adverse Drug Reactions (All Grade ≥ 20%)

	Inotuzumab ozogamicin		Standard therapy	
Adverse event	**All grades**	**≥ Grade 3**	**All grades**	**≥ Grade 3**
Infection	48%	28%	76%	54%
Thrombocytopenia	51%	42%	61%	59%
Neutropenia	49%	48%	45%	43%
Anemia	36%	24%	59%	47%
Leukopenia	35%	33%	43%	42%
Febrile neutropenia	26%	26%	53%	53%
Headache	28%	2%	27%	1%
Hemorrhage	33%	5%	28%	5%
Nausea	31%	2%	46%	0%
Abdominal pain	23%	3%	23%	1%
Hyperbilirubinemia	21%	5%	17%	6%
Transaminase increase	26%	7%	13%	5%
γ-glutamyltransferase increase	21%	10%	8%	4%

oped VOD received defibrotide; one patient died, two patients had symptoms resolved, and four patients had persistent symptoms. There were two treatment-related deaths from VOD after HSCT in the inotuzumab ozogamicin group. Median time to VOD after HSCT was 16 days; however, univariate analysis did not show VOD incidence association between the time of last inotuzumab ozogamicin dose and HSCT (Kantarjian et al., 2016).

Risk factors for VOD after HSCT include use of dual alkylator conditioning regimens, as well as elevated total bilirubin prior to HSCT. Other risk factors for VOD following inotuzumab ozogamicin are prior or ongoing liver disease, previous HSCT, increased age, and greater number of inotuzumab ozogamicin cycles. Due to the risk of VOD, inotuzumab ozogamicin should be limited to 2 cycles in patients who proceed to HSCT. Signs and symptoms of VOD, including hyperbilirubinemia, weight gain (one of the earliest signs), painful hepatomegaly, and ascites, should be monitored closely to allow for prompt diagnosis and management (Kebriaei et al., 2018; Pfizer, 2017). Liver function tests should be monitored prior to and after each dose of inotuzumab ozogamicin. Abnormalities in liver function tests may require therapy to be dose reduced or withheld (Kantarjian et al., 2016; Pfizer, 2017). A higher rate of non-relapse mortality after HSCT was reported in patients receiving inotuzumab ozogamicin compared with standard therapy (39% vs. 23%), with the most common causes being VOD and infection (Kantarjian et al., 2016; Pfizer, 2017).

DOSING AND ADMINISTRATION

Inotuzumab ozogamicin is given as an intravenous infusion over 1 hour at a rate of 50 mL/h. The dosing regimen is noted in Table 2. If patients do not achieve CR or CRi within 3 cycles, it is recommended to discontinue treatment. For patients who proceed to HSCT, only 2 cycles are recommended, although up to 6 cycles may be administered for those patients who are not proceeding to HSCT (Pfizer, 2017).

Patients should receive premedication with a steroid, antipyretic, and antihistamine prior to each dose. For patients with circulating lymphoblasts, cytoreduction with hydroxyurea, steroids, and/or vincristine to reduce peripheral blast count to less than 10,000/mm^3 is recommended prior to the first dose of inotuzumab ozogamicin (Pfizer, 2017).

Dose adjustments are based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) as noted in Table 3. Inotuzumab ozogamicin should not be interrupted for neutropenia or thrombocytopenia during a cycle. There are no recommended dose modifications for mild, moderate, or severe renal impairment and/or mild liver impairment. Safety in patients with end-stage renal disease with or without hemodialysis and/or moderate to severe liver impairment has not been determined (Pfizer, 2017).

IMPLICATIONS FOR THE ADVANCED PRACTITIONER

The goal of salvage therapy in relapsed or refractory ALL is to achieve a CR in hopes of proceeding to HSCT, which offers the only potentially curative option in these patients (Fielding et al., 2007; Kantarjian et al., 2016; Tavernier et al., 2007). Attempts to improve response rates by intensifying standard chemotherapy have been unsuccessful due to excessive toxicity (George et al., 2016; Kantarjian et al., 2012). Targeted therapies in ALL have demonstrated the ability to improve response

Table 2. Dosing Regimen of Inotuzumab Ozogamicin

Cycle	Dose	Cycle length
Cycle 1	0.8 mg/m^2 on day 1 and 0.5 mg/m^2 on days 8 and 15	21-day cycle (May extend to 28 days if in CR/CRi or to allow recovery from toxicity)
Subsequent cycle		
In CR/CRi	0.5 mg/m^2 on days 1, 8, and 15	28-day cycle
Not in CR/CRi	0.8 mg/m^2 on day 1 and 0.5 mg/m^2 on days 8 and 15	

Note. CR = complete remission; CRi = complete remission with incomplete hematologic recovery.

Table 3. Dose Modification of Inotuzumab Ozogamicin

Type of toxicity	Dose adjustment
Nonhematologic toxicity	
Total bilirubin > 1.5 × ULN and AST/ALT > 2.5 × ULN	Hold until bilirubin ≤ 1.5 × ULN and AST/ALT ≤ 2.5 × ULN
VOD or severe liver toxicity	Hold therapy permanently
Nonhematologic toxicity ≥ grade 2	Hold until recovery to grade 1 or baseline
Hematologic toxicity	
If prior to inotuzumab ozogamicin, ANC ≥ 1,000/mL or platelets ≥ 50,000 /mL	If ANC or platelets decrease, hold therapy until recovery to ANC ≥ 1,000/mL or platelets ≥ 50,000/mL. If ANC < 1,000/mL or platelets < 50,000/mL for > 28 days related to inotuzumab ozogamicin, discontinue therapy.
If prior to inotuzumab ozogamicin, ANC < 1,000/mL or platelets < 50,000/mL	If ANC or platelets decrease, hold next cycle until one of following occur: • ANC ≥ 1,000/mL and platelets ≥ 50,000/mL • ANC and platelets recover to baseline • Stable or improved disease and ANC, platelet decrease attributed to underlying disease

Note. ULN = upper limit of normal; AST = aspartate aminotransferase; ALT = alanine aminotransferase; VOD = veno-occlusive disease; ANC = absolute neutrophil count.

rates and avoid nonspecific toxicities (Kantarjian et al., 2016, 2017; Maude et al., 2014). Inotuzumab ozogamicin is a novel CD22-directed therapy option for patients with relapsed or refractory B-cell ALL. Use in patients with relapsed or refractory Ph-positive disease should be reserved for those who have failed treatment with at least one second-generation TKI. It has shown an advantage in CR rate, duration of remission, PFS, OS, and rate of subsequent HSCT.

Inotuzumab ozogamicin has been recently incorporated into the National Comprehensive Cancer Network (NCCN) Guidelines as a Category 1 recommendation for Ph-negative relapsed or refractory B-cell ALL and Category 2A recommendation for Ph-positive relapsed or refractory B-cell ALL (NCCN, 2017). Another targeted agent, blinatumomab (Blincyto), a bispecific CD19-directed CD3 T-cell engager is also an NCCN Category 1–recommended option for Ph-negative patients and a Category 2A–recommended option in Ph-positive patients (Amgen Inc., 2017; NCCN 2017).

In a phase III trial that included adults with relapsed or refractory Ph-negative B-cell ALL, blinatumomab was associated with a significantly higher CR (including full, partial, or incomplete hematologic recovery) when compared to standard chemotherapy (44% vs. 25%, $p < .001$). Results of this study also showed that blinatumomab use resulted in a significantly higher OS and duration of remission compared with standard chemotherapy (Kantarjian et al., 2017). In contrast, in the phase III study of inotuzumab ozogamicin, CR (including incomplete hematologic recovery) was 80.7%, subsequent HSCT was 41%, duration of remission was 4.6 months, and OS was 7.7 months (Kantarjian et al., 2016). It is worth noting that in the phase III trial of inotuzumab ozogamicin, more patients undergoing first salvage treatment were included compared with the phase III trial of blinatumomab (67% vs. 42.1%, respectively), possibly representing a less heavily treated population in the inotuzumab ozogamicin trial. Late first relapse, which is associated with a more favorable prognosis compared to relapse within 12 months, composed 43% of inotuzumab ozogamicin trial cohort, while none were included in the blinatumomab trial. In addition, the phase III trial of inotuzumab ozogamicin included fewer patients with previous HSCT (16% vs. 34.7%; Kantarjian et al., 2016, 2017).

The major warnings associated with blinatumomab use include cytokine release syndrome and neurologic toxicities, both of which can be potentially life-threatening. The major warnings associated with inotuzumab ozogamicin include potentially life-threatening hepatotoxicity, including VOD and increased risk of post-HSCT non-relapse mortality. In selecting the most beneficial targeted

therapy option in this patient population, the advanced practitioner must consider the potential benefits of each therapy, as well as side-effect profiles and potential logistical issues.

In clinical trials, neutropenia and thrombocytopenia were reported in 49% and 51% of patients, respectively. It is recommended to monitor complete blood counts prior to each dose, signs of infection, and hemorrhagic events. Infusion-related reactions are uncommon, occurring in 2% of patients in the phase III trial. Monitor patients during and for 1 hour following the end of the infusion for signs of infusion reactions (i.e., fever, chills, rash, and dyspnea). QTc prolongation was also rarely (2%) observed. Caution is advised in patients with a history of QTc prolongation, who are taking QTc prolonging medications, and with electrolyte disturbances. Monitor electrocardiograms and electrolytes prior to treatment, upon initiation of QTc prolonging medications, and as clinically indicated. Inotuzumab ozogamicin is also associated with embryo-fetal toxicity when administered to pregnant women. Advise women of reproductive potential to use effective contraception during treatment, for 8 months after, and to contact their provider if pregnancy is suspected. Advise men with partners of reproductive potential to use effective contraception during treatment and for 5 months after the last dose (Pfizer, 2017).

The cost of inotuzumab ozogamicin can be considerable and may represent a potential barrier to receiving this therapy. The average wholesale price (AWP) is approximately $77,642 per cycle based on a body surface area of 1.73 m^2 (AWP $22,440 per 0.9 mg vial; Truven Health Analytics, 2017). This does not include associated costs such as physician visits, laboratory assessment, drug administration, and supportive care. Patients can receive up to 6 cycles, further increasing the cost of therapy.

SUMMARY

Although current induction therapy in patients with ALL results in CR rates up to 90%, approximately 30% to 50% of patients will experience relapse (Kantarjian et al., 2010). Response rates to standard salvage chemotherapy remain unsatisfactory and use may result in excess toxicity. As CR is required prior to HSCT, the only potentially curative option in relapsed or refractory ALL, novel treatment strategies with the potential to improve response rates are needed. Inotuzumab ozogamicin has demonstrated the ability to significantly improve CR rates, MRD negativity, and survival compared with standard chemotherapy with tolerable toxicity and may be a more effective bridge to HSCT. Studies evaluating the safety and efficacy of inotuzumab ozogamicin in combination with chemotherapy in the front-line treatment of ALL, in combination with other targeted agents, in subsets of currently indicated populations, and in other B-cell malignancies are ongoing (see clinicaltrials.gov). Considering that inotuzumab ozogamicin will play an integral role in the management of relapsed or refractory B-cell ALL and potentially other indications, the advanced practitioner must be aware of important patient education information, toxicity management, and appropriate patient assessment.

Disclosure

The authors have no potential conflicts of interest to disclose.

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