Brief Communication

Obinutuzumab: A FDA approved monoclonal antibody in the treatment of untreated chronic lymphocytic leukemia

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Abstract

Chronic lymphocytic leukemia (CLL) is an adult lymphoid malignancy with a variable clinical course. There is considerable interest in the identification of new treatments, as most current approaches are not curative. While most patients respond to initial chemotherapy, relapsed disease is often resistant to the drugs commonly used in CLL and patients are left with limited therapeutic options. Obinutuzumab is recently approved in combination with chlorambucil for people with previously untreated CLL and is additionally being investigated in a large clinical program, including multiple head-to-head phase III studies compared with Rituxan in indolent non-Hodgkin's lymphoma and diffuse large B-cell lymphoma. In this article, author has made an attempt to review the therapeutic profile of this newly approved monoclonal antibody in the treatment of CLL.

Key words: Blood cancer, chronic lymphocytic leukemia, monoclonal antibody, obinutuzumab

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Introduction

Chronic lymphocytic leukemia (CLL) is one of the most common forms of blood cancer. It is expected that there were nearly 5000 deaths in the year 2013 from CLL in the United States.[1] CLL is characterized by the accumulation of monoclonal CD5+ mature B-cells in the peripheral blood (PB), lymph nodes and bone marrow.[2] Patients with CLL frequently present with immune disturbances, which constitute a notable feature of the disease compared to other chronic lymphoproliferative disorders.[3]

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Over the past 20 years, therapy for CLL has improved dramatically.[4] The frequency of complete responses achieved with traditional therapy using oral chlorambucil (single-agent alkylator) in the treated patients was <5%, while modern regimens using multi-agent chemoimmunotherapy can reliably produce complete responses in over 50% of patients. This notable improvement is primarily attributable to an increase in the number and activity of therapeutic agents recently made available to treat CLL, such as fludarabine,[5,6] a purine analogue-based chemotherapy agent as well as monoclonal antibodies rituximab[7] and alemtuzumab.[8] Novel combinations of these agents have emerged as effective new therapies for previously untreated patients. Clinical studies indicate that such combinations can induce higher response rates (including complete responses) than single-agent therapy.[9,10] Those patients who achieve a complete response have superior progression-free survival (PFS) compared with those who achieve only a partial response. However, there is still considerable interest in identifying new treatments as most current approaches are not curative.

Obinutuzumab is recently approved a monoclonal antibody, designed to attach to CD20, a protein found only on B-cells. It attacks targeted cells both directly and together with the body's immune system.[11]

Indications

Obinutuzumab has been approved by Food and Drug Administration in November 2013 for use in combination with chlorambucil for the treatment of patients with previously untreated CLL.

Recommended Dosage and Premedication

Obinutuzumab is administered by slow intravenous infusion following dilution of the 1000 mg/40 ml single use vial concentrate formulation. The dosing regimen for obinutuzumab is based on a 28 days treatment cycle. During cycle 1 patients receive a 100 mg dose on day 1, a 900 mg dose on day 2, and 1000 mg on day 8 and 15. Cycles 2–6 each consist of 1000 mg on day 1. In cycle 1, the first dose is split, in addition to withholding antihypertensive therapy for 12 h and administering required premedications [Table 1] prior to all obinutuzumab infusions, to minimize the risk of infusion related hypersensitivity reactions.[12]

Clinical Pharmacology

Mechanism of action

Obinutuzumab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B- and mature B-lymphocytes. Upon binding to CD20, obinutuzumab mediates B-cell lysis through (1) engagement of immune effector cells, (2) by directly activating intracellular death signaling pathways and/or (3) activation of the complement cascade. The immune effector cell mechanisms include antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis.[13]

Pharmacodynamics

In clinical trials in patients with CLL, obinutuzumab caused CD19 B-cell depletion (defined as CD19 B-cell counts <0.07 × 10^9/L). Initial CD19 B-cell recovery was observed in some patients approximately 9 months after the last obinutuzumab dose. At 18 months of follow-up, some patients remain B-cell depleted.

Although the depletion of B-cells in the PB is a measurable pharmacodynamic effect, it is not directly correlated with the depletion of B-cells in solid organs or in malignant deposits. B-cell depletion has not been shown to be directly correlated to clinical response. However, the potential effects of obinutuzumab on the QTc interval have not been studied.[12]

Pharmacokinetics

Based on a population pharmacokinetic (pop-PK) analysis, the geometric mean (CV%) volume of distribution of obinutuzumab at steady state is approximately 3.8 (23) L. The elimination of obinutuzumab is comprised of a linear clearance pathway and a time-dependent nonlinear clearance pathway. As obinutuzumab treatment progresses, the impact of the time-dependent pathway diminish in a manner suggesting target mediated drug disposition. Based on a pop-PK analysis, the geometric mean (CV%) terminal obinutuzumab clearance and half-life are approximately 0.09 (46%) L/day and 28.4 (43%) days, respectively.[12]

Specific Populations

It belongs to pregnancy category C; There are no adequate and well-controlled studies of obinutuzumab in pregnant women. Women of childbearing potential should use effective contraception while receiving obinutuzumab and for 12 months following treatment. Obinutuzumab should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.[12]

It is not known whether obinutuzumab is excreted in human milk. However, obinutuzumab is excreted in the milk of lactating cynomolgus monkeys, and human IgG is known to be excreted

Table 1: Premedication for obinutuzumab infusion to reduce IRR

Day of treatment cycle	Patients requiring premedication	Premedication	Administration
Cycle			
Day 1	All patients	Intravenous glucocorticoid: 20 mg dexamethasone or 80 mg methylprednisolone[a]	Completed at least 1 h prior to obinutuzumab infusion
Day 2		650-1000 mg acetaminophen Anti-histamine (e.g., diphenhydramine 50 mg)	At least 30 min before obinutuzumab infusion
Cycle 1			
Day 8	All patients	650-1000 mg acetaminophen	At least 30 min before obinutuzumab infusion
Day 15	Patients with an IRR (≥Grade 1) with the previous infusion	Anti-histamine (e.g., diphenhydramine 50 mg)	At least 30 min before obinutuzumab infusion
Cycles 2-6			
Day 1	Patients with a Grade 3 IRR with the previous infusion OR with a lymphocyte count >25×10^9/L prior to the next treatment	Intravenous glucocorticoid: 20 mg dexamethasone or 80 mg methylprednisolone[a]	Completed at least 1 h prior to obinutuzumab infusion

[a]Hydrocortisone is not recommended as it has not been effective in reducing the rate of infusion reactions. IRR: Infusion-related reaction

in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from obinutuzumab, a decision should be made whether to discontinue nursing or a discontinue drug, taking into account the importance of the drug to the mother.[12] Age did not affect the PKs of obinutuzumab.[12] Volume of distribution and steady state clearance both increased with body weight, however, the expected change in exposure does not warrant a dose modification.[12]

Based on the pop-PK analysis, baseline creatinine clearance (CrCl) >30 ml/min does not affect the PKs of obinutuzumab. Obinutuzumab has not been studied in patients with a baseline CrCl < 30 ml/min.[12] Obinutuzumab has not been studied in patients with hepatic impairment.[12]

Clinical Studies

Obinutuzumab was evaluated in a three arm, open-label, active control, randomized, multicenter trial (Study 1) in patients with previously untreated CD20+ CLL requiring treatment and had coexisting medical conditions or reduced renal function as measured by CrCl <70 ml/min. Patients with CrCl < 30ml/min, active infections, positive hepatitis B (hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [anti-HBc] positive, patients positive for anti-HBc could be included if hepatitis B viral DNA was not detectable) and hepatitis C serology, or immunization with live virus vaccine within 28 days prior to randomization were excluded from the trial. Patients were treated with chlorambucil control (Arm 1), obinutuzumab in combination with chlorambucil (Arm 2) or rituximab in combination with chlorambucil (Arm 3). The safety and efficacy of obinutuzumab was evaluated in a comparison of Arm 1 versus Arm 2 in 356 patients. However, data comparing Arm 2 versus Arm 3 are not available.

The majority of patients received 1000 mg of obinutuzumab on days 1, 8, and 15 of the first cycle, followed by treatment on the 1st day of five subsequent cycles (total of six cycles, 28 days each). The first dose of obinutuzumab was divided between day 1 (100 mg) and day 2 (900 mg), which was implemented in 45 patients. Chlorambucil was given orally at 0.5 mg/kg on day 1 and day 15 of all treatment cycles (1–6).

In Study 1, the median age was 73 years, 60% were male, and 95% were Caucasian. Sixty-eight percent had a CrCl < 70 ml/min and 76% had multiple coexisting medical conditions. Twenty-two percent of patients were Binet stage A, 42% were stage B, and 36% were stage C. The median estimated CrCl was 61 ml/min. Eighty-one percent of patients treated with obinutuzumab in combination with chlorambucil received all six cycles compared to 67% of patients in the chlorambucil alone arm.

The median PFS in the obinutuzumab in combination with chlorambucil arm was 23.0 months, and 11.1 months in the chlorambucil alone arm (median observation time 14.2 months) as assessed by independent review and is consistent with the investigator assessed PFS.[12]

Adverse Effects

The most common adverse reactions (incidence ≥10%) during the trial were: Infusion reactions, neutropenia, thrombocytopenia, anemia, pyrexia, cough, and musculoskeletal disorders.[12]

Warnings, Precautions and Contraindications

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with anti-CD20 antibodies such as obinutuzumab. HBV reactivation has been reported in patients who are HBsAg positive and also in patients who are HBsAg negative but are anti-HBc positive. Reactivation has also occurred in patients who appear to have resolved hepatitis B infection (i.e. HBsAg negative, anti-HBc positive, and hepatitis B surface antibody positive).

John Cunningham virus virus infection resulting in progressive multifocal leukoencephalopathy (PML), which can be fatal, was observed in patients treated with obinutuzumab. Consider the diagnosis of PML in any patient presenting with new onset or changes to preexisting neurologic manifestations. Obinutuzumab can also cause severe and life-threatening infusion reactions. Two-thirds of patients experienced a reaction to the first 1000 mg infused of obinutuzumab. Infusion reactions can also occur with subsequent infusions. Symptoms may include hypotension, tachycardia, dyspnea, and respiratory symptoms.

Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, and/or hyperphosphatemia from tumor lysis syndrome (TLS) can occur within 12–24 h after the first infusion. Patients with high tumor burden and/or high circulating lymphocyte count (>25 × 10^9/L) are at greater risk for TLS and should receive appropriate tumor lysis prophylaxis with antihyperuricemics (e.g., allopurinol) and hydration beginning 12–24 h prior to the infusion of obinutuzumab. Moreover, serious bacterial, fungal, and new or reactivated viral infections can occur during and following obinutuzumab therapy. Do not administer obinutuzumab to patients with an active infection. Patients with a history of recurring or chronic infections may be at increased risk of infection.

Obinutuzumab in combination with chlorambucil caused Grade 3 or 4 neutropenia in 34% of patients in the trial.

Patients with Grade 3–4 neutropenia should be monitored frequently with regular laboratory tests until resolution. Anticipate, evaluate, and treat any symptoms or signs of developing infection. Obinutuzumab in combination with chlorambucil also caused Grade 3 or 4 thrombocytopenia in 12% of patients in the trial. In 5% of patients, obinutuzumab caused an acute thrombocytopenia occurring within 24 h after the obinutuzumab infusion. In patients with Grade 3 or 4 thrombocytopenia, monitor platelet counts more frequently until resolution. Transfusion of blood products (i.e., platelet transfusion) may be necessary.

The safety and efficacy of immunization with live or attenuated viral vaccines during or following obinutuzumab therapy has not been studied. Immunization with live virus vaccines is not recommended during treatment and until B-cell recovery. There are no known contraindications to Obinutuzumab therapy. No formal drug interaction studies have been conducted with obinutuzumab.[12]

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