Obinutuzumab for previously untreated chronic lymphocytic leukemia

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Obinutuzumab was approved by the Food and Drug Administration in late 2013 for use in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL).[1,2] The approval was based on results of an open-label phase 3 trial that showed improved progression-free survival (PFS) with the combination of obinutuzumab plus chlorambucil compared with chlorambucil alone. Obinutuzumab is a monoclonal antibody that targets CD20 antigen expressed on the surface of pre B- and mature B-lymphocytes. After binding to CD20, obinutuzumab mediates B-cell lysis by engaging immune effector cells, directly activating intracellular death signaling pathways, and activating the complement cascade. Immune effector cell activities include antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis.

The efficacy data that supported the approval came from a comparison among 356 study patients who were randomized to receive obinutuzumab plus chlorambucil (n = 238) or chlorambucil alone (n = 118).[2] Data from larger groups of patients who received obinutuzumab–chlorambucil or rituximab–chlorambucil in the trial were not yet available. In the total trial,[3] 781 patients were randomized 1:2:2 to receive chlorambucil alone (n = 118), obinutuzumab–chlorambucil (n = 333), or rituximab–chlorambucil (n = 330). After 118 patients had been randomized to the chlorambucil-alone group, the group was closed, with 238 obinutuzumab–chlorambucil patients and 233 rituximab–chlorambucil patients constituting the combination treatment groups that were compared with chlorambucil alone. An additional 192 patients were then randomized to combination treatment (totals of 333 in the obinutuzumab–chlorambucil group and 330 in the rituximab–chlorambucil group). Treatment was administered in six 28-day cycles, with oral chlorambucil given at 0.5 mg/kg on days 1 and 15, obinutuzumab at 1,000 mg IV on days 1, 8, and 15 of cycle 1 and day 1 of cycles 2 to 6, and rituximab at 375 mg/m^2 IV on day 1 of cycle 1 and 500 mg/m2 on day 1 of cycles 2 to 6.

Patients had to have clinically meaningful coexisting conditions as indicated by a score > 6 on the Cumulative Illness Rating Scale (range, 0-56, with higher scores indicating worse health) or calculated creatinine clearance of 30-69 mL/min. The primary endpoint was PFS. In the labeling comparison of obinutuzumab–chlorambucil compared with chlorambucil alone, patients had a median age of 73 years, 60% were men, 95% were white, 68% had a creatinine clearance of < 70 mL/min (normal, men: 97-137 ml/min; women: 88-128 mL/min), 76% had multiple coexisting medical conditions, and 22%, 42%, and 36% were Binet stage A, B, and C, respectively. In total, 81% of the combination group and 67% of the chlorambucil-alone group received all 6 cycles of treatment.

In the larger trial population, there were no significant differences in baseline characteristics in the treatment

What's new, what's important

Obinutuzumab is a monoclonal antibody that targets CD20 antigen expressed on the surface of pre–B- and mature B-lymphocytes. It binds to CD20 and mediates B-cell lysis through immune effector cells, directly activating intracellular death signaling pathways, and activating the complement cascade. Obinutuzumab is indicated, in combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia.

Each dose of obinutuzumab is 1,000 mg, administered intravenously, with the exception of the first infusions in cycle 1, which are administered on day 1 (100 mg) and day 2 (900 mg). Since infusion reactions are common, it is important to premedicate with glucocorticoid, acetaminophen, and antihistamine. Patients with neutropenia should be considered for antimicrobial prophylaxis throughout the treatment period. Antiviral and antifungal prophylaxis also should be considered.

It is important to keep in mind that, hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with obinutuzumab. The most common adverse reactions were infusion reactions, neutropenia, thrombocytopenia, anemia, pyrexia, cough, and musculoskeletal disorder. The Food and Drug Administration's approval of obinutuzumab is a major advancement in the treatment of newly diagnosed CLL.

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How I treat previously untreated CLL

Therapy for chronic lymphocytic leukemia is undergoing drastic changes with the notable results seen with novel antibodies and kinase inhibitors. To expedite development of these novel regimens, we strongly urge patient participation in clinical trials whenever possible. Currently, our standard of care for the initial treatment of patients with CLL is to offer them treatment on intergroup trials.

The Alliance trial A041202 (http://www.cancer.gov/clinicaltrials/search/view?cdrid=750926&version=Patient) is directed toward previously untreated patients who are 65 years or older and who have symptomatic disease defined by the International Workshop on Chronic Lymphocytic Leukemia 2008 criteria. Patients can have received steroids or rituximab for autoimmune complications. This trial compares ibrutinib alone with ibrutinib–rituximab or bendamustine–rituximab. It is a randomized phase 3 study in which patients are assigned 1:1:1 to each arm. The bendamustine–rituximab arm has to cross over to ibrutinib at the time of progression. The primary endpoint of the trial is progression-free survival; the trial ultimately seeks to demonstrate benefit of targeted therapy over chemoimmunotherapy in elderly patients with CLL.

For younger and otherwise fit patients up to the age of 70, the ECOG-1912 randomized phase 3 trial (http://clinicaltrials.gov/ct2/show/NCT02048813) is comparing fludarabine, cyclophosphamide, and rituximab with ibrutinib and rituximab, with the primary endpoint being progression-free survival.

Both of these trials are available through the CTSU and are actively recruiting patients at multiple sites across the country. For patients who may not be eligible for either of these trials, we recommend referral to a specialized CLL center for an opinion regarding best treatment options either on an alternative clinical trial or standard of care.

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groups according to the comparisons of obinutuzumab–chlorambucil and chlorambucil alone, rituximab–chlorambucil and chlorambucil, or obinutuzumab–chlorambucil and rituximab–chlorambucil. The obinutuzumab–chlorambucil and rituximab–chlorambucil groups were generally balanced for age (median, 74 and 73 years), Cumulative Illness Rating Scale score (median, 8 in both groups), affected organ system or disorder (hypertension in 68% in both, cardiac in 51% and 50%, endocrine/metabolic in 55% and 49%), median calculated creatinine clearance (63 mL/min in both), Binet stage (A in 22% in both, B in 43% and 41%, C in 35% and 37%), unmutated IGHV (62% and 61%), and presence of del(17p) (7% in both).

Efficacy outcomes

For the labeling comparison, the median PFS on independent review was 23.0 months in the obinutuzumab–chlorambucil group, compared with 11.1 months in the chlorambucil-alone group (hazard ratio [HR], 0.16, P < .0001). The overall response rates were 75.9% and 32.1%, respectively, with complete response in 27.8% compared with 0.9%, and median duration of response was 15.2 and 3.5 months.

In the total trial, investigator-assessed PFS was significantly longer in both the obinutuzumab–chlorambucil group compared with the chlorambucil-alone group (26.7 vs 11.1 months, HR = 0.18, P < .001) and the rituximab–chlorambucil group compared with the chlorambucil-alone group (16.3 vs 11.1 months, HR = 0.44, P < .001). Investigator-assessed PFS was also significantly longer in the larger obinutuzumab–chlorambucil group compared with the larger rituximab–chlorambucil group (26.7 vs. 15.2 months, HR = 0.39, P < .001). The benefit of combination treatment compared with chlorambucil monotherapy was significant in all subgroup analyses for age, sex, Binet stage, baseline circulating lymphocyte count, Cumulative Illness Rating Scale score, calculated creatinine clearance, β2-microglobulin level, IGHV mutational status, and cytogenetics, except for del(17p). A significant benefit of obinutuzumab–chlorambucil over rituximab–chlorambucil was observed in all subgroups except among patients with del(17p) or other karyotypes.

Objective response was observed in 78% of the obinutuzumab–chlorambucil group, including complete response in 21%, compared with 65% of the rituximab–chlorambucil group, including complete response in 7% (P < .001). Rates of negative minimal residual disease were significantly greater with obinutuzumab–chlorambucil in both bone marrow (19.5% vs 3%, P < .001) and blood (38% vs 3%, P < .001).

At the time of analysis, median overall survival (OS) had not been reached in any treatment group. Obinutuzumab–chlorambucil was associated with a significant survival benefit compared with chlorambucil alone (9% vs 20% mortality; HR for death, 0.41; P = .002). There was no significant difference between rituximab–chlorambucil and chlorambucil alone (15% vs 20% mortality; HR, 0.66; P = .11) or between obinutuzumab–chlorambucil and rituximab–chlorambucil (HR, 0.66; P = .08).

Safety

For the labeling comparison between obinutuzumab–chlorambucil (safety population of 240) and chlorambucil alone (safety population of 116), the most common adverse events of any grade in combination group patients were infusion-related reactions (69% vs 0% in the chlorambucil group), neutropenia (40% vs 18%), and thrombocytopenia (15% vs 7%). The most common grade 3 or 4 adverse events

were infusion-related reactions (21% vs 0%), neutropenia (34% vs 16%), thrombocytopenia (11% vs 3%), and anemia (4% vs 5%). Infusion-related reaction symptoms included dyspnea, hypotension, nausea, vomiting, chills, flushing, and pyrexia. The most common grade 3 or 4 hematologic abnormalities were neutropenia (46% vs 27%), lymphopenia (40% vs 2%), leukopenia (36% vs <1%), and thrombocytopenia (14% vs 11%) and the most common grade 3 or 4 chemistry abnormalities were hyponatremia (8% vs 2%) and hyperkalemia (5% vs 2%). The incidence of infection was similar in the 2 groups, with infection occurring in 38% of the combination group and grade 3 or 4 infection occurring in 9%, with no fatalities. Grade 3 or 4 tumor lysis syndrome occurred in 2% of the combination group and in 0% of the chlorambucil alone group.

In the full trial reporting, adverse events were more common with obinutuzumab–chlorambucil than with rituximab–chlorambucil or chlorambucil alone. Grade 3 or higher adverse events occurred in 73% of the obinutuzumab–chlorambucil group (safety population of 241), compared with 50% of the chlorambucil group (safety population of 116), 56% of the rituximab–chlorambucil group (safety population of 225) that was compared with the chlorambucil group, and 70% of the obinutuzumab–chlorambucil group (safety population of 336), compared with 55% of the rituximab–chlorambucil group (safety population of 321).

For the obinutuzumab–chlorambucil group compared with the rituximab–chlorambucil group, the most common grade 3 or higher adverse events were neutropenia (33% vs 28%), infections (12% vs 14%, including pneumonia in 4% vs 5% and febrile neutropenia in 2% vs 1%), and infusion-related reactions (20% vs 4%). All grade 3 or 4 infusion reactions in the obinutuzumab–chlorambucil group occurred during the first infusion. Grade 3 or 4 thrombocytopenia (10% vs 3%) and leukopenia (4% vs 1%) were also more common with obinutuzumab–chlorambucil. Grade 3 or 4 tumor lysis syndrome occurred in 2% vs 0%. Serious adverse events occurred in 39% vs 32%, with the most common being infection (13% vs 14%), neoplasms (6% in both), and infusion-related reaction (10% vs 2%). Death due to an adverse event occurred in 4% vs 6% of patients.

Obinutuzumab is marketed as Gazyva injection for IV infusion by Genentech Inc. It carries a boxed warning for hepatitis B virus reactivation, which has resulted in fulminant hepatitis, hepatic failure, and death in some cases, and for progressive multifocal leukoencephalopathy, which has resulted in death. Obinutuzumab also has warnings/precautions for infusion-related reactions, tumor lysis syndrome, neutropenia, thrombocytopenia, and immunization.

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