Fourth approved indication for ofatumumab in chronic lymphocytic leukemia

The recent decision by the US Food and Drug Administration to approve ofatumumab in combination with fludarabine and cyclophosphamide in relapsed disease marks a fourth approved indication for this drug in patients with chronic lymphocytic leukemia (CLL). Ofatumumab is a fully human monoclonal antibody that targets the CD20 protein on the surface of B cells, first approved for the treatment of CLL back in 2009.

The latest approval was based on the phase 3, open-label, randomized COMPLEMENT-2 trial in 365 patients with relapsed CLL across 18 countries. The results of this trial have not yet been published, but were presented at the 20th Congress of the European Hematology Association in 2015. Patients were randomly assigned in a 1:1 ratio to receive either ofatumumab in combination with fludarabine and cyclophosphamide, or the chemotherapy doublet, fludarabine and cyclophosphamide, alone. Ofatumumab was administered intravenously at a dose of 300 mg on day 1 of the first cycle, followed by a 1,000-mg dose on day 8 and from day 1 of subsequent cycles. Fludarabine and cyclophosphamide were given at their standard doses; 25 mg/m^2 and 250 mg/m^2, respectively, on days 1-3 every 28 days for up to 6 cycles.

Blood sampling, lymph node examination, spleen and liver measurement, and constitutional symptom evaluations were performed monthly during treatment and follow-up assessment of survival and disease status was performed 1 month after therapy and every 3 months for 5 years. CT scans were performed on patients achieving complete or partial response at 3 months post-therapy and a bone marrow exam was required to confirm complete response.

The primary endpoint was progression-free survival (PFS), and triplet therapy demonstrated a more than 50% increase in PFS compared with chemotherapy alone. The median PFS was 28.9 months, compared with 18.8 months in the triplet and doublet arms, respectively (hazard ratio [HR], 0.67; P = .0032). Patients in the ofatumumab arm also experienced significantly longer overall response rates (84% vs 68%, respectively) and improved time to progression (42.1 months vs 26.8 months, respectively; HR, 0.63; P = .0036). Median overall survival was numerically greater in patients receiving triplet therapy (56.4 months vs 45.8 months), but did not reach statistical significance.

The safety profile of ofatumumab was as expected from previous studies in CLL. Adverse events (AEs) were experienced in 93% of patients in the ofatumumab arm, compared with 85% of patients treated with chemotherapy alone. AEs experienced by 5% or more patients treated with triplet therapy included neutropenia, thrombocytopenia, anemia, nausea, leukopenia, and vomiting. The rate of grade 3 and higher AEs was 74% in the ofatumumab arm, compared with 69% in the control arm. There were lower rates of grade 3 or higher thrombocytopenia and anemia in patients treated with triplet therapy, but

What's new, what's important

Ofatumumab, a fully human monoclonal antibody that targets the CD20 protein on the surface of B cells, was recently approved in combination with fludarabine and cyclophosphamide for treating relapsed CLL. The approval was based on a phase 3 trial in which patients received either ofatumumab in combination with fludarabine plus cyclophosphamide or fludarabine plus cyclophosphamide alone. Median PFS in the ofatumumab group was 28.9 months (controls, 18.8 months). Study group patients also had significantly longer ORRs (84% vs 68%) and improved time to progression (42.1 vs 26.8 months), and their OS was numerically greater, but not significant. Ofatumumab was administered intravenously at 300 mg on day 1 of the first cycle, followed by a 1,000-mg dose on day 8 and from day 1 of subsequent cycles. Fludarabine and cyclophosphamide were given at the standard doses.

In study group patients, 93% experienced adverse events (controls, 85%), with ≥5% experiencing neutropenia, thrombocytopenia, anemia, nausea, leukopenia, and vomiting; and 74% having AEs of grade 3 or higher (control group, 69%). Ofatumumab has a boxed warning about HBV reactivation and PML, so patients must be screened for hepatitis B infection before therapy initiation and for neurological signs or symptoms during therapy. Other warnings for serious, even fatal, AEs include infusion reactions, manifesting as bronchospasm, dyspnea, edema, hypertension, and others. Some patients are at risk for TLS. Complete blood counts should be regularly monitored during and after ofatumumab therapy, increased in regularity in patients developing grade 3 or 4 cytopenias. Patients should not be immunized with live viral vaccines because their safety has not been studied in ofatumumab.

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Report prepared by Jane De Lartigue, PhD. JCSO 2016;14(11):447-449. ©2016 Frontline Medical Communications. doi:10.12788/jcso.0303

Mechanism of action: ofatumumab

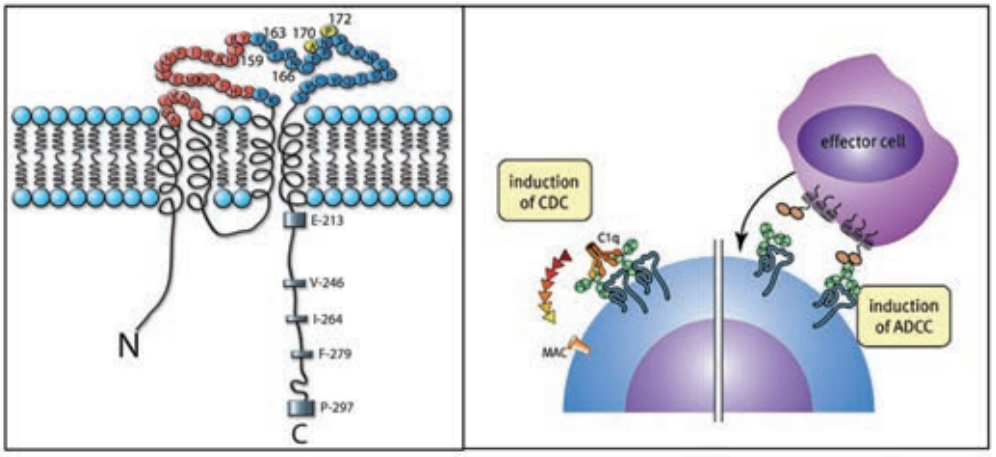
Targeting CD20 protein in a unique way

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in the United States and, except for allogeneic stem-cell transplantation, for which not all patients are eligible, there is currently no curative treatment. CD20 has proved to be an important therapeutic target in other B-cell malignancies, validated by the success of the monoclonal antibody rituximab as the first CD20-targeting drug to enter the clinic, but it is less effective in patients with CLL.

CD20 is a protein that is highly expressed on the surface of B cells throughout their development, but is not found on the surface of mature plasma cells. Its precise function remains unclear, though it is thought to play a role in B-cell activation and growth. It is also highly expressed on all B-cell malignancies; however, expression levels are lower in CLL, which may partly explain the reduced efficacy of rituximab.

Ofatumumab is a novel CD20-targeting monoclonal antibody with a unique way of binding to CD20. The CD20 protein crosses the plasma membrane several times, creating 2 extracellular loops. Although rituximab binds to the larger of the 2 loops, ofatumumab also binds to the smaller loop, which is situated closer to the cell membrane. It's thought that this proximity improves the ability of ofatumumab to engage the complement system.

Monoclonal antibodies can kill cancer cells via a number of different mechanisms, including antibody-dependent cellular cytotoxicity (ADCC), in which the fragment crystallizable domain of the antibody engages the fragment crystallizable receptors on the surface of immune effector cells, and complement-dependent cytotoxicity, whereby the antibody activates the complement system, which involves a cascade of proteins that assemble a membrane attack complex that inserts itself into the cell membrane of the foreign cell, causing cell lysis and death.



Ofatumumab is a fully human monoclonal antibody that targets CD20 on the surface of B cells. It binds to a unique epitope on the CD20 protein, which increases the potency of its complement-dependent cytotoxicity. This may make it more effective in the treatment of B cell malignancies like chronic lymphocytic leukemia that express lower levels of CD20. Reproduced with permission: Ruuls SR et al. Novel human antibody therapeutics: the age of the Umabs. Biotechnol J. 2008;3(9-10):1157-1171.

Preclinical studies have shown ofatumumab to be a particularly potent inducer of complement-dependent cytotoxicity, in addition to its effects on ADCC. Ofatumumab has also been shown to bind more strongly to CD20 than rituximab does, which may also help to increase the death of CD20-expressing cancer cells, particularly low-CD20-expressing cells such as those found in patients with CLL.

higher rates of neutropenia and infusion-related reactions.

Ofatumumab is marketed as Arzerra by Genmab and Novartis. It carries a boxed warning about the risks of hepatitis B virus (HBV) reactivation and progressive multifocal leukoencephalopathy (PML), both potentially fatal side effects. All patients should be screened for hepatitis B infection, by measuring both viral surface antigens and core antibody levels, before the start of ofatumumab therapy. Ofatumumab treatment should be immediately discontinued in patients who develop HBV reactivation and resumed only after consulting an expert in HBV management. Patients should also be monitored for new onset of or changes in pre-existing neurological signs or symptoms and, if PML is suspected, ofatumumab should be discontinued.

The prescribing information details further warnings and precautions for these and several other AEs. Serious and often fatal infusion reactions, manifesting as bronchospasm, dyspnea, edema, hypertension, and others can occur and are more common with the first 2 infusions. Temporary interruption or withdrawal of treatment along with medical management should be considered. If an anaphylactic reaction occurs, ofatumumab treatment should be immediately and permanently discontinued.

Patients with high tumor burden and/or high circulating

lymphocyte counts are at increased risk of tumor lysis syndrome (TLS). Prophylaxis with anti-hyperuricemics and hydration beginning 12-24 hours prior to ofatumumab treatment can be considered. If TLS occurs, these treatments should be administered, electrolyte abnormalities should be corrected and renal function monitored.

Complete blood counts should be monitored at regular intervals during and after ofatumumab therapy and the frequency of monitoring should be increased in patients who develop grade 3 or 4 cytopenias. Patients should not receive immunization with live viral vaccines as their safety has not been studied in patients receiving ofatumumab.

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