M. Montillo

Dept of Haematology
Niguarda Ca' Granda
Hospital Milan, Italy

Ofatumumab: a second generation anti-CD20 monoclonal antibody in chronic lymphocytic leukemia

The successful use of monoclonal antibodies (mAb) in the treatment of human disease has steadily been growing the last decade. Rituximab, a human-mouse chimeric anti-CD20 antibody, was the first mAb for anti-lymphoma therapy approved. It was introduced as monotherapy and is now commonly used in combination with chemotherapy for first and subsequent lines of therapy in follicular non-Hodgkin lymphoma (FL) and chronic lymphocytic leukemia (CLL). However, a subgroup of patients does not respond, indicating a clear unmet need to explore alternative antibodies non-cross resistant to rituximab.

One of the most advanced of the new anti-CD20 mAb is ofatumumab which is currently in clinical development for CLL and lymphoma. Ofatumumab, developed from human Ig transgenic mice, is a fully humanized anti-CD20 monoclonal antibody that has been shown, preclinically, to be exceptionally active and produce a strong CDC by more efficiently binding C1q to the surface of the CD20-positive cell.[1] This newer antibody interacts with a different epitope of the CD20 molecule on B cells, which is located in the smaller extracellular loop of CD20[2] and releases only very slowly from the target. It is hypothesized that the efficacy of ofatumumab is due to a slower off-rate and more stable CD20 binding in comparison to rituximab. Ofatumumab has an antibody-dependent cellular cytotoxocity similar to rituximab, but it delivers a stronger complement-dependent cytotoxicity even towards lymphoma cells with a low CD20 antigen density and a high number of CD55 and CD59 complement inhibitory molecules on the cell membrane. In laboratory tests, ofatumumab has been found to be superior to rituximab with respect to its ability to induce lysis in different B-cell lines and to kill fresh CLL cells resistant to rituximab. Such lytic activity was not seen with rituximab. Ofatumumab has a potentially reduced immunogenicity compared with the other products which will be particularly helpful in autoimmune disease where 30–50% of patients have responded to rituximab with the development of an anti-Ab response (HACA).[3] Initial phase I/II clinical data in relapsed/refractory FL was presented by Hagenbeek *et al.*[4] Forty patients were given escalated doses of Ofatumumab from 300 mg to 1000 mg intravenously weekly for 4 weeks, obtaining an ORR of 63% with 57% response in patients previously treated with rituximab without reported dose-limiting toxicity. Coiffier *et al.* reported the result of a multicen-

ter dose-escalating study including 33 patients with relapsed or refractory CLL reporting significant depletion of $CD19^+CD5^+$ cells by all patients. Three cohorts of 3 (A), 3 (B), and 27 (C) patients received 4, once weekly, infusions of Ofatumumab at the following doses: (A) one 100 mg and three 500 mg; (B) one 300 mg and three 1000 mg; (C) one 500 mg and three 2000 mg. The maximum tolerated dose was not reached. Ofatumumab was found to be well tolerated in patients with CLL to doses up to 2000 mg. The response rate at this dose was 50% (13/26), 1 patient having a nodular partial remission and 12 patients a partial remission. Further data on the use of ofatumumab as a single agent in fludarabine-refractory CLL patients were reported by Osterborg *et al.* An interim analysis of 138 patients refractory to fludarabine and alemtuzumab or to fludarabine with bulky lymphadenopathy showed an ORR of 44 and 51%, respectively.[6] The median OS was about 14 months for the first group and 15 months for the latter. Patients received 8 weekly infusions of ofatumumab followed by 4 monthly infusions (Dose 1, 300 mg; Doses 2-12, 2000 mg). These preliminary data show that ofatumumab may represent an active treatment option for patients with very poor prognosis who have failed standard treatments. Ofatumumab is currently being investigated in various clinical phase III trials treating lymphoma, CLL and rheumatoid arthritis.

References

1. Teeling JL, French RR, Cragg MS, et al. Characterization of new human CD20 monoclonal antibodies with potent cytolytic activity against non-Hodgkin lymphomas. Blood 2004;104:1793-800.
2. Teeling JL, Mackus WJ, Wiegman LJ, et al. The biological activity of human CD20 monoclonal antibodies is linked to unique epitopes on CD20. J Immunol 2006; 177:362-71.
3. Eisenberg, R, Looney, RJ. The therapeutic potential of anti-CD20 "what do B-cells do?". Clin Immunol 2005; 117:207-13.
4. Hagenbeek A, Gadeberg O, Johnson P, et al. First clinical use of ofatumumab, a fully human anti-CD20 monoclonal antibody in relapsed or refractory follicular lymphoma: results of a phase I/II trial. Blood 2008;111: 5486-95.
5. Coiffier B, Lepretre S, Pedersen LM, et al. Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a phase 1-2 study. Blood 2008;111:1094-100.
6. Osterborg A, Kipps TJ, Mayer J, et al. Ofatumumab (HuMax-CD20), a novel CD20 monoclonal antibody, is an active treatment for patients with CLL refractory to both fludarabine and alemtuzumab or bulky fludarabine-refractory disease: results from the planned interim analysis of an international pivotal trial blood (ASH Annual Meeting Abstracts). 2008;112:328.