Ublituximab, an Optimized Anti-CD20 Monoclonal Antibody, Demonstrates Greater NK-Mediated ADCC Than Rituximab in Waldenstrom’s Macroglobulinemia Patients Supporting a Therapeutic Strategy with Ublituximab

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INTRODUCTION

Anti-CD20 monoclonal antibody (mAb) therapy is an important therapeutic option in the treatment of Waldenström’s Macroglobulinemia (WM), exhibiting an ORR up to 55% when used as monotherapy (Gentz, Leuk Lymphoma, 2004).

NK cells are involved in mAb therapy by an antibody-dependent cellular cytotoxicity (ADCC) mechanism through their FcγRlla (CD16) receptor. In this study, we have evaluated the ADCC functional capacities of NK cells in the presence of ublituximab (TGTX-1101 or LFB-R603), an optimized anti-CD20 mAb exhibiting a low fucose content, in comparison to rituximab.

METHODS

Blood samples from 40 untreated or without ongoing treatment WM patients and from 30 age-matched healthy donors (Ctl) were collected to quantify CD16 expression (clone 3B8, Quantibrite®) on NK cells and/or to measure their functional capacities. Patients were divided in two groups relative to the presence (WM clones) or absence (WM clone-) of blood clonal B cells. NK cell degranulation was assessed by the surface expression of CD107α on NK cells after incubation of PBMC with or without Raji CD20+ target cells in the presence of anti-CD20 mAbs at 10 and 1,000 ng/ml. ADCC experiments were performed using a chromium assay with purified NK cells and autologous B cells or Raji target cells, in the presence of anti-CD20 mAbs at 1 and 100 ng/ml.

RESULTS

In the presence of Raji cells, at low concentration, a significantly greater amount of CD107α expression was observed with ublituximab compared to rituximab (P<0.01), regardless of patient’s groups. In contrast, at the highest concentration, similar effects were obtained with both anti-CD20 mAbs.

In the presence of autologous B cells, degranulation assays revealed that none of the NK cells from WM clone- patients exhibited degranulation, irrespective of the anti-CD20 mAb or its concentration. More importantly, NK cells of 3/8 WM clone+ patients exhibited CD107α+ NK cells in the presence of both concentrations of ublituximab. In contrast, with rituximab only 1/8 patients expressed CD107α+ NK cells, and only at the highest concentration. Of note, similar frequency and cell-surface expression level of CD107α on NK cells were detected in both patient groups.

CONCLUSION

These results show that, as previously described in CLL, ublituximab is more efficient than rituximab in inducing ADCC at low doses, in the presence of Raji cells. More importantly, our results suggest that ublituximab could be more efficient than rituximab both to induce NK cell degranulation and ADCC in the presence of autologous peripheral tumor cells. These findings highlight a new putative role of this optimized anti-CD20 mAb in the control of WM, and prompt further investigations in a large cohort of WM patients. A Phase III trial with single agent ublituximab in patients with rituximab released / refractory NHL, including WM patients is currently ongoing.

J.F. Prost, C. de Romeuf and R. Urbain are employed by LFB, whose potential product is studied in the present work. M. Le Garff-Tavernier, C. de Romeuf, Y. Leblond, V. Vieillard and H. Merle-Bérál have filed patent applications (PCT/FR2012/051395), owned by LFB Biotechnologies and Université Paris 6 Pierre et Marie Curie, covering use of ublituximab in Waldenström’s Macroglobulinemia. C. de Romeuf, J.F. Prost have filed patent applications (PCT/FR2005/003123) owned by LFB Biotechnologies, covering use of ublituximab in B cell-lymphoma. L. Herbi and P. Debre have no relevant conflicts of interest to disclose.

Figure 1: Potential mechanisms of action of anti-CD20 mAbs

mAbs have several potential mechanisms of action, including antibody-dependent cellular cytotoxicity (ADCC), which involves recruitment of effector cells with FcγR, like NK cells.

adapted from Cheson et al, NEJM, 2008

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Statistical analyses were performed with Prism 5 software. Intergroup comparisons were assessed with the nonparametric Kruskal-Wallis test, with the Dunn’s postanalysis test. Significance defined by P less than 0.05 with a two-tailed test. *P<0.05; **P<0.01