LFB-R603 (UBLITUXIMAB), A THIRD-GENERATION MONOCLONAL ANTI-CD20 ANTIBODY, DISPLAYS ADDITIVE ANTITUMOR ACTIVITY WITH ANTILEUKEMIC CHEMOTHERAPEUTIC AGENTS IN MOUSE XENOGRAFT MODELS

Abstract
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INTRODUCTION

LFB-R603, a next generation anti-CD20 antibody currently in clinical development, is characterized by a specific glycosylation pattern containing a high percentage of non-fucosylated antibody molecules at the Fc site. This pattern of glycosylation increases the affinity of antibodies for human FcγR-mediated cell-mediated cytotoxicity (ADCC) by human FcγRIIIa-expressing effector cells. A phase I clinical trial with this antibody in Chronic Lymphocytic Leukemia (CLL) patients is now completed and clinical development is planned to be expanded to other Non-Hodgkin’s Lymphomas (NHL) such as follicular and mantle cell lymphomas, as a single agent and in combination with chemotherapeutic agents.

In this context, the antitumor efficacy of LFB-R603 was studied in combination with conventional chemotherapeutic agents in two models of NHL developed in immune-deficient mice.

Materials and Methods

Lymphomas (NHL) such as follicular and mantle cell lymphomas, as a single agent and in combination with chemotherapeutic agents.

Tumor cell lines, derived from a patient with follicular lymphoma (RL cells) or a patient with mantle cell lymphoma (NCEB cells), were xenografted in mice by subcutaneous injection. Tumor-bearing mice were treated intravenously once a week for 3 or 4 weeks with the anti-CD20 antibodies used alone or in combination with suboptimal doses of cyclophosphamide (CTX) 50 mg/kg or bendamustine (BEN) 30 mg/kg. Times of injection are indicated on the graphs by arrows. Tumors were measured twice a week and tumor volumes were calculated to compare the kinetics of tumor growth. Each point of the graphs represent the median +/- SEM of 10 or 4 animals for the RL or the NCEB model respectively. Primary tumor volume (TV) was calculated according to the formula $TV = \frac{4}{3} \pi r^3$, volume of a sphere, calculating $r$ as the average between the two measurements of the tumor.

Medium tumor growth inhibition (MTGI) for volume (TV) or for tumor mass (TM) was calculated according to the NCI formula [1-(TV-X)/TVX] or [1-(TV-X)/TV], where Y is the day of median day of euthanasia in the control group and X is the day of first administration of treatment. Statistical analysis was performed by ANOVA testing (Statistics 6.0).

CONCLUSION AND PERSPECTIVES

LFB-R603 displayed greater antitumor activity as compared to rituximab in two different non-clinical in vivo models of NHL, namely follicular and mantle cell lymphoma. Moreover, additive effects were obtained when LFB-R603 was combined with chemotherapeutic agents such as cyclophosphamide and bendamustine in the FL model. Therefore, clinical development of LFB-R603 in combination with bendamustine or cyclophosphamide in follicular lymphoma and in mantle cell lymphoma could be relevant.

The combination of LFB-R603 or rituximab at 60 mg/kg with cyclophosphamide enhanced the effect observed with the antileukemic agent alone and the additive effect was similar for the two antibodies, as a delay of 13 days in tumor growth was observed for both combination-treated groups compared with the cyclophosphamide-treated group (p=0.0001).

In the NCEB model, LFB-R603 and rituximab injected once weekly up to 3 weeks displayed a dose-related anti-tumor activity. A higher activity of LFB-R603 compared to rituximab was observed at all tested doses (3, 10, 30 and 40 mg/kg) (p<0.05).

Background and Study Objectives

LFB-R603 displays higher anti-tumor activity than rituximab (RTX)

Anti-tumor activity in a follicular lymphoma model

LFB-R603 displays higher anti-tumor activity than rituximab (RTX) in combination with bendamustine (BEN)

Anti-tumor activity in a mantle cell lymphoma model

CONCLUSIONS

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