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Targeted monoclonal antibody therapy in chronic lymphocytic leukemia

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Abstract

Chronic lymphocytic leukemia (CLL) is still regarded as an incurable disease with a great need for developing new therapies and optimizing existing treatment options. The development of targeted therapy, i.e. therapy interfering with specific molecules needed for carcinogenesis and tumor growth, is rapidly evolving. The aim of this thesis is to delineate the clinical and immunological effects of targeted therapy with alemtuzumab in CLL patients.

In the first study, a long-term follow-up of patients who received alemtuzumab as first-line therapy was conducted. The results were compared with matched historic controls. Median time to treatment failure (TTTF) was 28 months for the alemtuzumab treated compared with 17 months for the control group (not significant). Additionally, our data showed that, despite long-lasting T cell suppression, alemtuzumab treated patients had comparable rates of infectious complications and incidence of Richter transformation as the matched controls.

In the second study, patients with advanced CLL, who all had severe transfusion-dependent and multi-agent refractory autoimmune hemolytic anemia (AIHA), received alemtuzumab as salvage therapy. All patients responded with a $\geq$ 2.0 g/dl rise in hemoglobin (Hb) concentration, in the absence of further transfusions, after a median time of 5 weeks. No further AIHA episodes were observed during long-term follow-up. CLL responses were achieved in all but one patient. These results suggest that alemtuzumab may be effective in the treatment of severe AIHA in patients with progressive CLL who have failed to respond to conventional therapy.

In the third study, the type, severity and duration of side-effects as well as efficacy of subcutaneous (SC) alemtuzumab, without dose-escalation, was evaluated in advanced-stage relapsed CLL patients. A starting dose of 30 mg SC was well tolerated and all but one injection-site reactions were grade 1/2. A 75% overall response rate (ORR) and long TTTF (median 20 months for responding patients) was obtained, suggesting that optimal selection of advanced-phase CLL patients for alemtuzumab therapy may result in a high response rate and durable remissions.

In the fourth study, T cell receptor B-variable (TCR-BV) gene usage in CD4 and CD8 T cells was assessed by real-time PCR, as well as complementarity-determining region 3 (CDR3)-length polymorphism, before and after therapy in patients with CLL who received alemtuzumab as first-line therapy. Our results indicate that perturbations of the T cell repertoire following alemtuzumab are complex and not reflected by changes in the total number of CD4/CD8 T cells only. A restricted CDR3 pattern present prior to therapy became even more restricted after treatment, followed by a normalisation of CD4 repertoire during long-term follow-up.

In the fifth study, we investigated the incidence and clinical relevance of subclinical virus reactivations and serological changes in CLL patients who received alemtuzumab as first-line therapy and compared the results with fludarabine-based combination therapy. Except for CMV, there was no increased incidence of virus reactivation compared with the fludarabine + cyclophosphamide +/- rituximab treated controls. All reactivations resolved spontaneously. The number of significant antivirus IgG decreases or increases did not differ significantly between the two treatment groups.

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