Tumor necrosis factor and lymphotoxin-alpha genetic polymorphisms and risk of relapse in childhood B-cell precursor acute lymphoblastic leukemia: a case-control study of patients treated with BFM therapy

ABSTRACT

Our results do not suggest a major role of the investigated genetic polymorphisms with regard to risk of relapse in standard- and intermediate-risk childhood B-cell precursor ALL treated according to BFM protocols.

INTRODUCTION

Background Tumor necrosis factor (TNF) and lymphotoxin-α (LT-α ; formerly TNF-β) are cytokines with pleiotropic biological activities including, for example, the induction of programmed cell death and the regulation of immune cell proliferation and differentiation. In a variety of studies, plasma levels of TNF or LT-α have been associated with outcome of certain autoimmune and infectious diseases as well as solid and hematologic malignancies. Of interest, the secretion of TNF and LT-α is believed to be influenced by genetic polymorphisms within their genes located tandemly on the long arm of chromosome 6 within the MHC class III region. One of the best described of these polymorphisms is located at nucleotide position-308 within the TNF promoter region and affects a consensus sequence for a binding site of the transcription factor AP-2. Guanine at position-308 defines the common TNF1 allele and adenine the less common TNF2 allele. With regard to the LT-α gene, a polymorphism at nucleotide position 252 within the first intron was reported to influence LT-α plasma levels. This single nucleotide polymorphism (A252G) affects a phorbol ester-responsive element and distinguishes two alleles that have been designated LT-α (10.5 kb) and LT-α (5.5 kb). Both the TNF2 and the LT-α (5.5 kb) allele have been shown to correlate with elevated TNF or LT-α plasma levels. Besides a more severe outcome of autoimmune or infectious diseases and of particular interest to us, the TNF2 and the LT-α (5.5 kb) alleles have been associated with an adverse outcome in lymphoid malignancies. In the present study, we genotyped a matched case-control study group of 64 relapsed and 64 non-relapsed patients with childhood acute lymphoblastic leukemia (ALL) for the above described genetic polymorphisms within the TNF and LT-α genes in order to assess their predictive potential with regard to relapse in childhood ALL.

CONCLUSION

Conclusions In a matched case-control group of 64 relapsed and 64 successfully treated childhood B-cell precursor ALL patients (all at standard or intermediate risk), the TNF gene polymorphism at nucleotide position -308 and the LT-α gene polymorphism at nucleotide position +252 were not significantly related with risk of ALL relapse. Our results do not suggest a major role of the investigated genetic polymorphisms with regard to risk of relapse in childhood B-cell precursor ALL of standard and intermediate risk treated according to BFM protocols.