Abstract

Wilms' tumor gene 1 (*WT1*) is highly expressed in acute leukemia and other hematological malignancies. It has been therefore suggested as a potential universal marker of minimal residual disease (MRD), particularly in patients with acute myeloid leukemia (AML). Due to controversial results of some of the studies, the role of *WT1* in MRD follow-up and WT1 prognostic significance remain unclear.

WT1 protein is produced in more than 36 different isoforms. These variants have distinct, partially overlapping functions and their ratio is supposed to influence the final effect of *WT1*. However, despite the increasing number of studies, the clinical impact of *WT1* and its isoforms in acute leukemia have not yet been elucidated.

We established a unique qPCR method to assess the expression pattern of the main 4 *WT1* isoforms. Using this method, we determined the ratio of *WT1* variants in the samples of patients with AML, myelodysplastic syndrome (MDS) and healthy controls. Our data showed that this pattern can distinguish among particular hematological malignancies, but lacks a prognostic significance.

Within our international study group we determined the prognostic significance of total *WT1* expression in childhood AML. Based on our results of a large cohort of patients we can conclude that *WT1* expression at diagnosis is not an independent prognostic factor for the outcome of pediatric AML. Mutation analysis of this cohort showed no impact of *WT1* mutations on the quantification of its expression.

In addition to evaluating the prognostic significance of *WT1* at diagnosis, we also investigated the impact of pre/post-transplantation levels of *WT1* expression in patients with childhood AML undergoing stem-cell transplantation (SCT). In contrast to some previously published data, we could not observe any clinical relevance of either pre/post SCT expression of *WT1* or monitoring of *WT1* expression after SCT in pediatric AML.

In the majority of studies on childhood AML, *WT1* detection is realized by analysis of bone marrow (BM) samples, although there are some suggestions that peripheral blood (PB) is more suitable for this purpose. The results of our analysis suggest that PB can provide more useful information on MRD in childhood AML.

Although we could not confirm the correlation of WT1 mRNA and protein level, it has been shown that the studies on the clinical relevance of *WT1* that were based on the analysis of mRNA level provide relevant and conclusive data.

Lastly, analysis of patients with MDS supported the involvement of *WT1* quantification into the diagnostic algorithm that should help in differential diagnosis between patients with refractory cytopenia and aplastic anemia.

In conclusion, this study has brought several novel aspects of the role of *WT1* gene and its isoforms in hematopoiesis and leukemogenesis and underlined the importance of *WT1* isoform expression pattern in malignant transformation of hematopoietic cells.