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Significance of Wilms' Tumor Gene 1 as a Biomarker in Acute Leukemia and Solid Tumors

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Abstract

Wilms' tumor gene 1 (*WT1*) is a zinc finger transcriptional regulator with crucial functions in embryonic development. Originally *WT1* was described as a tumor suppressor gene, but later studies have shown oncogenic properties of *WT1* in a variety of tumors. Because of its dual functions in tumorigenesis, *WT1* has been described as a chameleon gene. In this thesis, the significance of WT1 as a biomarker was investigated in acute myeloid leukemia (AML), clear cell renal cell carcinoma (ccRCC), ovarian carcinoma (OC) and childhood B-cell precursor acute lymphoblastic leukemia (BCP-ALL).

Previous studies have suggested that expression of *WT1* is a potential marker for detection of minimal residual disease (MRD) in AML. We aimed to define expression of *WT1* as an MRD marker in AML. In adult AML patients we found that a reduction of *WT1* expression in bone marrow (≥ 1-log) detected less than 1 month after diagnosis was associated with an improved overall survival (OS) and freedom from relapse (FFR). In peripheral blood a reduction of *WT1* expression (≥ 2-log) detected between 1 and 6 months after treatment initiation was associated with an improved OS and FFR.

WT1 harbor pathogenic genetic variants in a considerable proportion of AML and T-lymphoblastic leukemia (T-ALL), but mutations have not been reported in BCP-ALL. We aimed to evaluate the clinical impact of *WT1* mutations and single nucleotide polymorphisms (SNPs) in BCP-ALL. Pathogenic mutations in the *WT1* gene were rarely seen in childhood BCP-ALL. However, five *WT1* SNPs were identified. In survival analyses, *WT1* SNP rs1799925 was found to be associated with worse OS, indicating that *WT1* SNP rs1799925 may be a useful marker for clinical outcome in childhood BCP-ALL. We also explored whether *WT1* mutations and SNPs in ccRCC could be used as biomarkers for risk and treatment stratification. We therefore examined whether SNPs or mutations in *WT1* were associated with *WT1* expression and clinical outcome. Sequencing analysis revealed that none of the previously reported *WT1* mutations were found in ccRCC; however, we identified six different *WT1* SNPs. Our data suggest that pathogenic *WT1* mutations are not involved in ccRCC, and the prognostic significance of *WT1* SNPs in ccRCC is considerably weak. However, a favorable OS and disease-specific survival were found in the few cases harboring the homozygous minor allele.

OC has a poor prognosis, and early effective screening markers are lacking. Serous OCs are known to express the WT1 protein. Overexpressed oncogenic proteins can be considered potential candidate antigens for cancer vaccines and T-cell therapy. It was therefore of great interest to investigate whether anti-WT1 IgG antibody (Ab) measurements in plasma could serve as biomarkers of anti-OC response. We found limited prognostic impact, but the results indicated that anti-WT1 IgG Ab measurements in plasma and WT1 staining in tissue specimens could be potential biomarkers for patient outcome in the high-risk subtypes of OCs.

In conclusion, the results of this thesis indicate that *WT1* gene expression can provide information about MRD of patients with AML, and *WT1* SNP rs1799925 may be used as a biomarker for predicting clinical outcome in childhood BCP-ALL. In ccRCC, the prognostic significance of *WT1* SNPs is weak and limited to the subgroup of patients that are homozygous for the minor allele. In OCs anti-WT1 IgG Ab measurement in plasma and WT1 staining in tissue specimens could possibly be used as biomarkers for predicting patient outcome in the high-risk subtypes of OCs.

Keywords
Wilms' tumor gene 1, biomarker, leukemia, renal cell carcinoma, ovarian carcinoma

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