Research Article

Role of dickkop^{f-1}in chronic lymphocytic leukemia

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Abstract
Introduction: Chronic lymphocytic leukemia (CLL) is a hematological neoplasm, which is characterized by clonal proliferation and accumulation of small round B lymphocytes within the bone marrow, peripheral blood, lymph nodes and spleen (Chen et al., 2016). Dickkopf-1 (Dkk1) IS AN INHIBITOR of the Wnt-β −catenin pathway (D'amico et al., 2016). The clinical significance of Wnt pathway inhibition with dickkop^{f-1}(DKK-1) was shown in various cancers (pamuk et al., 2015). Wnt signaling was demonstrated to be activated in chromic lymphocytic leukemia (CLL). It is demonstrated that the Wnt pathway inhibitor DKK-1 was decreased in CLL (pamuk et al., 2015).
Patients and methods: The present study included 75 subjects, 50 patients with chronic lymphocytic leukemia diagonosed by B.M. examination and immunophenotyping. They were selected from minia oncology center and minia university hospital, from august 2016 to February 2017, and 25 apparently healthy subjects as control. All patients and controls were subjected to laboratory analysis including CBC, immunophenotyping, ESR, liver and kidney function tests, LDH, bone marrow examination for patients only. Serum DDK-1 was measured to all subjects. A commercially available ELISA kit was used to check serum DKK-1. **Results:** We found that decreases DKK-1 may be a good biomarker for detection of CLL disease and its progression with great sensitivity and specificity.
Key Words: CLL: chronic lymphocytic leukemia, DKK-1 :dickkof-1.

Introduction
chronic lymphocytic leukemia (CLL) is a hematological neoplasm, which is characterized by clonal proliferation and accumulation of small round B lymphocytes within the bone marrow, peripheral blood, lymph nodes and spleen (CHEN etal., 2016). The immunoheno type of neoplastic CLL cells is characterized by the coexpression of cluster of differentiation CD23, weak expression of CD20, CD79b and surface immunoglobulin (Ig), as well as negative CD10 and FMC7 expression (CHEN et al., 2016).

Dickkop^{f-1} (DKK1) is an inhibitor of the Wnt-β-catenin pathway (D'AMICO et al., 2016). Which regulates key cellular functions including proliferation, differentiation, migration, genetic stability, apoptosis, and stem cell renewal (Pai et al.,2017). DKK-1 competitively binds to the Wnt co-receptors LRP5/6, leading to degradation of the β-catenin complex (D'Amico et al., 2016).

It was stated that the Wnt signaling pathway active in embryonic cells and adult stem cells; howere, it became progressively turned off in more differentiated cells. In addition, it was demonstrated that some mature cells acquired the Wnt signaling pathway during the process

of tumorigenesis. The clinical significance of Wnt pathway inhibition with dickkop^{f-1}(DKK-1) was shown in yarious cancers (Pamuk et al., 2015). Wnt signaling was demonstrated to be activated in chronic lymphocytic leukemia (CLL). It is thought to be responsible for the extended survival of CLL cells in vivo (Filipovich et al., 2010). It is demonstrated that the Wnt pathway inhibitor DKK-1was decreased in CLL (Pamuk et al., 2015).

Aim of work
This work aims to study the role of DKK-1in the pathogenesis of chronic lymphocytic leukemia and its prognostic value in the disease.

Patients and methods
The present study included 75 subjects,50 patients with chronic lymphocytic leukemia diagnosed by B.M. examination and immunophenotyping. They were selected from minia oncology center and minia university hospital, from August 2016 to February 2017,

and 25 apparently healthy subjects as control.

All patients and controls were subjected to laboratory analysis including CBC, immune-phenotyping, ESR, liver and kidney function test, LDH, bone marrow examination for patients only. Serum DKK-1 was measured to all subjects. A commercially available ELISA kit (Glory science co, ltd) was used to check serum DKK-1.

Results

Our study demonstrated the following:

	Group I New Diagnosed (n=25)	Group II on treatment (n=25)	Group III Control (n=25)	P value		
Dkk-1 Median IQR	917 (318.8-3151.5)	4271 (2153.5-6141.5)	5890 (2722-8866.5)	<0.001*		
				Ivs II	**Ivs III**	**II Vs III**
				0.003*	<0.001*	0.114

variable	Optimal cutoff	Auc	P value	sensitivity	specificity	ppv	npv	accuracy
Dkk-1	≤2241	0.848	<0.01*	72	84	81.1	75	78

Discussion

Dickkop[f-1] is an endogenous endogenous negative regulator of wnt/β-catenin signaling and accumulating evidence indicates that higher serum levels of DKK1 are correlated with poor prognosis of various types of cancer (kim et al., 2017).

The present study has showed that DKK-1 decreased with disease progression and elevation indicates better prognosis .

In the present study, there was significant decrease in serum DKK-1 on comparing group II and control group.

The present study has showed that DDK-1 decreased with the disease progression and elevation of its levels indicates better prognosis. The results of the present work were in agreement with (Pamuk et al., (2015) who tested whether DKK-1 level could be of clinical or prognostic significance in 36 CLL patients, after a median follow-up of 48 months, 13 CLL patients who died had significantly lower DKK-1 than those who were alive.

Pamuk et al., (2015) demonstrated that the wnt pathway inhibitor DKK-1 was decreased in CLL patients that might be explained with disease pathogenesis and enhanced Wnt signalling in CLL.

Also results of Liu et al., (2006). Chim et al., (2008) and seeliger et al., (2009) were in agreement with our study. They suggested that wnt signaling is constitutively activated in CLL B lymphocytes in association with methylation of multiple soluble Wnt antagonist genes (such as DKK-). Methylation of these soluble Wnt antagonist genes in primary CLL marrow samples suggests an important role in CLL pathogenesis and down regulation of these Wnt antagonists (such as DKK-1) proved to be a possible reason for activated Wnt signaling in CLL.

Filipovich et al., (2010) reported that DKK-1 was similar in healthy and CLL cells by estimation of the expression of DKK1 by western blot and real-time PCR. B cells from patients with CLL and healthy donors were incubated with recombinant DKK1 and reported a normal expression level of Wnt/β-catenin signaling inhibitor DKK1, which was similar in healthy and CLL cells, although DKK-1 expression was shown on CLL cells, Wnt signaling pathway could not be inactivated with the addition of DKK-1 , therefore DKK-1 was a therapeutically unfavorable target in CLL.

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