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*Review Article*

# Leptin and its receptor in hematologic malignancies

Tian-Jie Han[1,2], Xin Wang[1]

[1]*Department of Hematology, Shandong Provincial Hospital, Shandong University, Jinan 250021, Shandong, China;* [2]*Department of Hematology, Tai'an Central Hospital, Tai'an 271000, Shandong, China*

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**Abstract:** Leptin is an adipocyte-derived cytokine coded by the obese gene, not only regulates metabolism, but also participates in hematopoiesis. Aberrant leptin levels in patients with hematologic malignancies were observed and associates with clinical characters, such as body mass index (BMI), gender, blast cell percentage. Leptin concentrations alter while diseases progress or remission. Leptin receptor is expressed in hematopoietic CD34+ stem cells, erythrocytes, lymphocytes, blast cells and samples in leukemia and lymphoma patients. The adipokine stimulates cell proliferation, cytokine secretion and protects malignant cells from apoptosis through Janus kinase-signal transducer and activator of transcription (JAK-STAT), mitogen-activated protein kinase and extracellular signal activated kinase 1/2 (MAPK/ERK1/2), or 3 kinase (PI3K) signaling pathways. These findings indicate leptin signaling possibility take part in occurrence, progression and prognosis of hematologic malignancies. This article reviews leptin/leptin receptor expression and the correlations with clinical characters, treatment and prognosis in myeloid and lymphoid neoplasms.

**Keywords:** Leptin, leptin receptor, hematologic malignancies, signaling pathway, pathogenesis

## Introduction

Adipocytes secrete active biological molecules, mainly including leptin, resistin and adiponectin [1]. Leptin is the most widely studied adipocyte-derived hormone, not only modulating nutrition, metabolism and immune homeostasis, but also participating in hematopoiesis and neoplasmas genesis [2, 3]. Leptin exerts actions through its specific receptor which is localized to the cell membrane and present in a variety of hematopoietic cells, such as hematopoietic progenitor cells, erythropoietic, myeloid and lymphoblastic cell lines [4-7]. Apart from the regulation of normal hematopoiesis, leptin and its receptor have been implicated in hematopoietic malignancies pathogenesis and progression. Thus, it is important to determine the expression of leptin and its receptor in malignant blood diseases and the effect of leptin/leptin receptor signaling on blast cells of these disorders.

### *Structure and biological function of leptin and its receptor*

Leptin identified by Zhang is the product of obese (ob) gene [8]. Mature leptin is a secreted protein composed of 146 amino acids. When the typical structure was solved, leptin was detected four anti-parallel α helices (A, B, C, and D). Two conserved cysteine residues (C96 in the CD loop and C146 as the C-terminal residue) forms a solvent-exposed disulfide bridge, that is essential for structural stability and biological activity [9, 10]. The structure of leptin has significant similarity to the structures of granulocyte colony-stimulating factor (G-CSF) and to the interleukin (IL)-6 family of cytokines [11].

Leptin receptor belongs to the class I cytokine receptor superfamily, is a single membrane-spanning receptor, which exhibits homology to the gp130 signal-transducing subunits of receptors for IL-6, G-CSF, and leukemia inhibitory factor (LIF) receptor [12]. There are at least six isoforms of leptin receptor (OBRa, OBRb, OBRc, OBRd, OBRe and OBRf) resulting from alternative gene splicing. OBRb with the longest cytoplasmic domain length, is the only receptor isoform capable of full signal transduction [13, 14]. When leptin bind leptin receptor, several signaling pathways are activated, including JAK/STAT, MAPK/ERK1/2

and PI3K signaling pathway [15, 16]. Leptin-deficient ob/ob mice and leptin receptor deficient db/db mice display a series of marked abnormalities secondary to the lack in leptin/leptin receptor signal, such as obesity, reproductive disorders, thymic atrophy, defective immune responses and so on [17].

Numerous of studies linked leptin with variety of malignancies, focusing on the ability of leptin to affect proliferation, apoptosis, migration and invasion of tumor cells, angiogenesis and immunodeficiency [18-20]. Leptin is present in human peripheral blood, cord blood and bone marrow blood. Evidences have shown that leptin/leptin receptor signal plays important role in proliferation, differentiation, and function of hematopoietic progenitor cells and mature blood cells in vitro and vivo [21, 22]. Therefore, leptin and its receptor may affect the development, progression and prognosis of hematopoietic malignancies. Blocking leptin signaling pathway could become potential therapy for certain neoplastic hematologic disorders.

*Role of Leptin and its receptor in hematologic malignancies*

A number of studies provided serum leptin levels and leptin receptor expression in blast cells in myeloid and lymphoid malignancies. The effects of leptin/leptin receptor on hematologic malignances and the mechanisms have been reported.

## Myeloid neoplasms

*Acute myeloid leukemia (AML)*

In AML patients, serum leptin level is not higher than that in healthy controls, while the adipokine may promote AML cells growth, inhibit blast cells apoptosis and increase cytokine production. Leptin receptor is expressed in AML cells and samples of newly diagnosed patients. Anti-leptin receptor treatment decrease angiogenesis in AML rats.

Results of several studies showed that serum leptin levels in AML patients were significantly lower than healthy controls and had negative correlation with BM blast cells, total WBC counts and sLDH [23, 24]. While no notable difference of serum leptin concentrations between patients with de novo AML and healthy controls were found in another two studies [25, 26]. Leptin level in AML was correlated with Body Mass Index (BMI) and gender, but not chemotherapy [23, 27].

Leptin receptor was expressed in various human AML cell lines, particularly in K562 and MO7E cells [28]. Moreover constitutive expression of leptin receptors was observed in primary leukemic cells and newly diagnosed AML samples. Compared to short isoform, the incidence of long isoform expression was higher. Refractory and relapsing AML showed stronger expression of both isoforms than primary cases [28, 29]. Additionally human recombinant leptin (r-leptin) upregulated the expression of leptin receptor short isoform of AML blasts, whereas r-leptin had no similar effect on the total or long isoforms [7].

Leptin promotes proliferation of AML cell lines, such as HEL [30], MO7E, TF-1 and blasts from primary AML patients in dose dependent manner [28]. Transfection of leptin receptor specific RNAi blocked the phosphorylation of STAT-3 and ERK1/2, significantly decreased the growth of HEL cells induced by leptin [30]. Also, leptin protected MO7E and TF-1 cells from the apoptosis resulting from withdrawal of GM-CSF [28]. On the other hand, leptin may stimulate leukemic cell proliferation by promoting angiogenesis. After subcutaneous injections of anti-rat leptin receptor monoclonal antibody (mAb) to AML rat models for 3 weeks, substantial decrease in the density of microvessels was observed, accompanying marked reduction of leukemic cells in bone marrow [31]. In AML rats with a mutated leptin receptor, no effect on leukemic cell growth or angiogenesis was found. Furthermore, leptin increases cytokines production in AML blasts. Researchers cultured leukemic cells derived from AML patients with different concentrations of leptin, then IL-1β and IL-6 levels were determined. The result showed IL-1βand IL-6 levels increased in a dose dependent manner. Moreover, AML blasts treated with leptin 2 μg/mL secreted much more IL-1β, IL-6, TNF and GM-CSF than negative controls [7, 23]. (Clinical reports on leptin/leptin receptor for AML are summarized in **Table 1**).

*Acute promyelocytic leukemia (APL)*

Leptin and its receptor were found intensively related with PML/RARα expression in APL. In normal hematopoiesis, the promyelocytes expressed short isoform of leptin receptor at

**Table 1.** Recent clinical trials of Leptin/Leptin receptor for AML

| Author (year) | Circulating leptin of newly diagnosed cases (compared with healthy controls) | Circulating leptin of treated patients (compared with untreated cases) | Correlation with clinical characters | Expression of leptin receptor (compared with healthy controls) |
|---|---|---|---|---|
| Konopleva, M. [6] | comparable | | BMI (positively correlated) | increased |
| Bruserud, O [23] | decreased | comparable | | |
| Aref, SI [24] | decreased | | BM blast cells sLDH (negatively correlated) | |
| Yilmaz, M [25] | comparable | comparable | | |
| Tavil, B [26] | comparable | increased | | |
| Pamuk, GE [27] | comparable | comparable | | |
| Foss, BL [28] | | | VEGF (positively correlated) | |
| Gorska, E [29] | | | | comparable |
| Nakao, T [37] | | | | increased |

BMI: body mass index, BM: bone marrow, sLDH: serum lactic dehydrogenase, VEGF: vascular endothelial growth factor.

**Table 2.** Recent clinical trials of Leptin/Leptin receptor for ALL

| Author (references) | Circulating leptin of newly diagnosed cases (compared with healthy controls) | Circulating leptin of treated patients (compared with untreated cases) | Correlation with clinical characters | Expression of leptin receptor (compared with healthy controls) |
|---|---|---|---|---|
| Aref, S [24] | increased | | BM blast cells percentage, blood total WBCs counts, sLDH (positively correlated) | |
| Tavil, B [26] | decreased | increased | | decreased |
| Pamuk, GE [27] | decreased | | | |
| Gorska, E [29] | | | | decreased |
| Moschovi, M [50] | increased | increased | negatively related: BMI, HDL-C; positively related: leukemic burden, LDH, TG | |
| Wex, H [51] | comparable | increased | | |
| Wasik, M [52] | comparable | | | |

BM: bone marrow, WBC: white blood cells, sLDH: serum lactic dehydrogenase, BMI: body mass index, HDL-C: high-density lipoprotein cholesterol, TG: triglycerides.

low level, while primary acute promyelocytic leukemia (APL) cells expressed high levels of both isoforms [28]. Compared with the APL cell line NB4 cells, the primary APL cells expressed much higher level of OB-R long isoform mRNA. Both isoforms were expressed in newly diagnosed and recurrent APL cells. OB-R long isoform and PML/RARα mRNA expression level had positive correlation [28, 32]. To investigate the effect of leptin derived from BM adipocytes on with PML/RARα expressing APL cells, researchers cultured mesenchymal stem cell (MSC)-derived adipocytes with PML/RARα expressing APL cells, the coculture system reduced APL cell apoptosis induced by all-*trans* retinoic acid (ATRA) and doxorubicin, they also linked the direct cell-to-cell interactions to STAT3 and MAPK pathways. When NB4 cells were co cultured with adipocyte differentiated MSCs, the phosphorylation of STAT3 and MAPK increased. Once treated with chimeric OB-R, the phosphorylation were partially reversed.

*Chronic myelogenous leukemia (CML)*

Studies showed leptin level was not upregulated in CML, whereas the value altered with response to imatinib treatment. The median serum leptin level in CML patients at diagnosis had no sufficient difference with respect to control subjects, and there were no statistical correlations between leptin and leukocyte counts, neutrophil counts, basophils, sLDH and Sokal score [33]. Whereas the imatinib therapy may result in leptin value alteration. After imatinib therapy, serum leptin levels were found higher than normal in most patients (8/9) and lower in one patient. While the value was recovered normally when the patient interrupted imatinnib after cytogenetic relapse. The trend to this adipokine improvement was found in three patients accepted intermittent administration [34]. Study of Alonci et al [33] also showed leptin concentrations of all patients in molecular remission after imatinib therapy were significant higher than the baseline levels.

Expressions of the leptin receptors were downregulated in PBMC from CML patients, particularly OB-Rb level was undetectable by using RT-PCR. For CML cell lines, total OB-R and OB-Ra isoforms expressions were found to be significantly lower in Meg-01 cells than K562 cells [35]. While study of Diaz-Blanco et al showed the leptin receptor gene of CML patients in chronic phase was significantly upregulated in primary CML CD34+ cells at the transcriptional level, about 3.12 folds higher than normal controls. No significant difference between the gene expression of CD34+ cells from peripheral blood and bone marrow of CML patients was found [36]. When CML develop into blast crisis, higher expression was observed than in chronic phase [37]. Imatinib therapy may not affect leptin receptor isoform expressions [35].

*Myelodysplastic syndrome (MDS)*

With respect to MDS, leptin and its receptor seem to be linked to clinical classification and prognosis. One case control study reported that no significant difference of circulating leptin levels between MDS patients and healthy controls. In comparison with refractory anemia (RA), refractory anemia with ring sideroblast (RARS) and chronic myelomonocytic leukemia (CMML), refractory anemia with excess blasts (RAEB) and refractory anemia with excess of blasts in transformation (RAEB-t) have higher leptin levels. Furthermore higher leptin were found in International Prognostic Scoring System (IPSS) high-risk subgroup than those in the intermediate- and low-risk subgroups and in MDS with a poor prognosis karyotype than MDS with a normal or good prognosis MDS karyotype. The researchers divided leptin levels in quartiles. Compared to subjects in the lowest quartile, patients in the third quartile had decreased risk of MDS [38].

Circulating soluble leptin receptor (sOB-R) levels and Leptin Index (FLI) calculated as the ratio of leptin to sOB-R in patients with MDS and control subjects were described in one study [38]. Patients exhibited lower serum levels of sOB-R and similar level of FLI in comparison with controls. Among MDS, sOB-R was negatively associated with BMI. On the contrary, FLI was positively correlated with weight, BMI, fetuin-A and insulin. FLI levels expressed by control-defined quartiles exhibited a negative correlation with the risk of MDS. Moreover, FLI increased in RAEB compared to RA and CMML, in MDS with an intermediate prognosis karyotype than in MDS with a normal or good prognosis karyotype [39]. Serum leptin and sOB-R levels detected in study of Tsiotra et al [40], were found slightly higher in MDS. The expression of

the leptin receptor long isoform was significantly lower in MDS than healthy individuals while the short isoform tended to be higher in MDS.

Together, most studies showed that serum leptin level and leptin receptor expression were not higher than healthy population in myeloid neoplams. Leptin plays an important role in promoting the proliferation of AML cells, protecting AML cells from apoptosis and increasing secretion of cytokines. Leptin receptor expression elevates when disease progress. Moreover, it possibly correlates with clinical types.

*Lymphoid neoplasms*

Leptin receptor is expressed in normal CD4+, CD8+ T cells, NK cells and B cells. Ob/ob mice were observed immunosuppression and thymic atrophy [41]. Depending on different activation, T cells are divided into naïve, memory and effector T cells in naïve T cells, leptin increases cell proliferation and IL-2 production through MAPK and PI3K pathways. Although leptin rarely affects the proliferation of memory T cells, it has significant role in promoting a bias towards Th1 cell response [42]. Compared with wild-type mice, CD4+ T-cell polarization in vitro was suppressed in cells from *ob/ob* mice. The down-regulated expression of key transcription factors for Th1 and Th2 polarization, T-bet and GATA-3 may explain the protection of *ob/ob* mice in Th1 and Th2-dependent inflammation [43]. In effector T cells (Teffs), there is a strong link between autocrine secretion of leptin and mammalian target of rapamycin (mTOR) activation. The blockade of leptin/leptin receptor signaling, results in inhibited proliferation of Teffs which is induced by impaired mTOR activity [44]. On the other hand, regulatory T (Treg) cells secrete leptin and expressed high levels of leptin receptor. Leptin acts as a negative signal in proliferation of Treg cells. After neutralization with leptin mAb IL-2 dependent proliferation of Treg cells was increased in vitro [45].

Regarding to Natural killer (NK) cells, the critical mediators of anti-tumor immunity, leptin protects NK cells from apoptosis during development in mouse bone marrow, db/db mice exhibited impaired NK cells activity [46, 47]. Leptin stimulated metabolic activity of human NK-92 cells dose-dependently. High leptin dose increased production of granzyme B and TRAIL, while decreased perforin expression. Moreover, at 100 and 200 ng/ml, leptin enhanced NK-92 cell cytotoxicity against K562-EGFP and MDA-MB-231-EGFP target cells [48]. Compared with the T cells, B cell seems more sensitive to leptin antiapoptotic effect. Lam et al [49] demonstrated leptin protected B cell from apoptosis by activating B-cell lymphoma 2 (Bcl-2) and cyclin D1. There are at least two mechanisms for leptin to up-regulate Bcl-2 and cyclin D1 expression: activating their promoters and suppressing miRNAs that target the putative 3'untranslated regions (UTR) of Bcl-2 and cyclin D1 mRNAs. These findings indicate that leptin plays a key role during lymphocyte development and differentiation, and it could be an important signal transduction factor in The pathogenesis of lymphoid neoplasms.

*Acute lymphoblastic leukemia*

Present studies indicate significant difference between leptin concentration in peripheral blood and in bone marrow of ALL patients. The plasma leptin levels in peripheral blood were significantly higher in ALL patients than controls, especially in unfavorable group. There were positive significant correlations between BM blast cells percentage, blood total WBCs counts, sLDH and plasma leptin levels [24]. Data from children with ALL of B-cell origin also revealed heightened levels of serum leptin. Delta mean leptin was positively correlated with leukemic burden. Compared with baseline values, leptin levels were much lower before the end of maintenance phase of chemotherapy [50]. While the leptin concentrations in bone marrow-plasma of childhood ALL patients at diagnosis were significantly lower than the levels of healthy controls. At complete hematologic remission, leptin levels on average had increased almost 3 folds, and were consequently in the same range as the plasma of healthy donors [51]. Another study detected both blood serum and bone marrow leptin levels in children with ALL-B and ALL-T, the leptin concentration was higher in the blood than that in bone marrow, whereas it was comparable in children with AML [52].

The expression of the leptin receptor was low in ALL cell lines and primary blasts. One study assessed membrane expression of leptin receptor in children with ALL using flow cytometry method [29]. The number of T and B blast

cells expressed Ob-R was smaller than T and B-cells from bone marrow of control subjects. In subgroup analysis, the percentages of T CD8+ Ob-R+ blasts from ALL-T subpopulation were much lower in comparison with T CD8+ Ob-R+ normal bone marrow cells. Results of reverse transcriptase polymerase chain reaction (RT-PCR) from another study showed the gene expression rate of newly diagnosed cases was 33%, compared with 71% for patients at remission and 100% for controls. Immunohistochemical analysis on samples from ALL patients (n=3) revealed leukemic blasts did not express the leptin receptor, whereas surrounding lymphocytes exhibited strong staining [51]. Regarding to ALL cell lines, the B-cell derived cells (ALL, ARH-77, IM-9, RPMI1788, HS-Sultan, Raji) exhibited very low, even absent leptin receptor expression, compared with relative higher expression of the OB-Ra. While the significantly higher OBR-total/Rb/Ra expression was observed in the T-cell acute lymphoblastic leukemia Jurkat cells [7]. (Clinical reports on leptin/leptin receptor for ALL are summarized in **Table 2**).

*Non-Hodgkin lymphoma (NHL)*

Serum leptin levels are decreased in untreated NHL compared with healthy controls. The value appears increased after disease remission [54-57]. One multiethnic nested case control study showed leptin was related with the risk of total NHL and follicular lymphoma (FL), as well as adjustment for body mass index (BMI) [54]. Although Pamuk et al [27] reported leptin concentration negatively correlate with international prognostic index (IPI), the other studies found no statistic correlation with any reference mark for valuating prognosis [55, 58]. In diffuse large B cell lymphoma (DLBCL), specimens expressed significantly higher ObR levels than in reactive lymphoid hyperplasia (RLH) [59]. ObR expression exhibited positive correlation with that of p-STAT3, p-AKT and antiapoptotic marker XIAP in DLBCL patients, but no significant association with age, gender, extra nodal infiltrations, clinical stage, LDH level, B-symptoms and IPI [59, 60]. The in vitro study demonstrated that leptin promoted DLBCL cell lines, SUDHL4, SUDHL5 and SUDHL10 cells proliferation and suppressed apoptosis through PI3K/AKT pathway. Treatment with Ob-R specific small interference RNA or PI3K inhibitor LY294002, abrogated leptin-induced cell proliferation and anti-apoptosis in DLBCL cells [60].

*Chronic lymphocytic leukemia (CLL)*

Serum leptin levels in patients with CLL and the correlations with prognostic parameters are controversial in different studies. The serum leptin levels evaluated through enzyme-linked immunosorbent assay (ELISA) in patients with CLL were higher than healthy subjects [27]. In addition, leptin level had a positive correlation with the poor prognostic marker -CD38 level. Whereas, another study focused on B-cell CLL [53] indicated that serum leptin values determined by the method of radioimmunoassay were decreased when compared to the control group. Both univariate and multivariate analysis showed higher leptin levels were associated with a decrease in B-CLL risk. Moreover leptin had weak statistically positive association with LDH and β2 microglobulin (r=0.22 and 0.27 respectively). However, the association between leptin and LDH became nonsignificant, when coefficients were adjusted for age and BMI. There were no significantly correlation between leptin levels and different stages of B-CLL (Binet classification) and CD38 level. Both isoforms (the long and short isoforms) were negatively expressed at mRNA level in samples from patients with CLL [28].

*Hodgkin lymphoma (HL)*

There are very few studies describing the association between leptin and HL. One article evaluated serum leptin levels in children with lymphoma, including 15 cases with HL, found the values in HL children was comparable with those in healthy controls. Furthermore, no significant difference was detected between pretreatment and post-treatment levels of leptin in patients with HL. At the end of follow-up, all patients achieved remission except for one who died of disease progression, while leptin levels were found no effect on HL survival [55]. That is different from the results of another study which reported international prognostic score (IPS) in HL patients had negative correlations with leptin level [27].

*Multiple myeloma (MM)*

Serum leptin levels were apparently higher in newly diagnosed MM cases than in healthy

individuals in recent studies [27, 61-63]. In patients achieved disease plateau after standard treatment (the vincristine-adriamycin-dexamethasone regimen or melphalan-prednisolone and monthly infusions of biphosphonates) leptin concentrations were decreased remarkably [63]. However for patients accepted thalidomide therapy, the adipokine levels were revealed no significant difference between responders and non-responders to the thalidomide taking. In patients with relapse, no particular adipokine pattern was revealed [62]. Serum leptin levels seemed to positively correlate with IgG levels, ESR 1st hour and LDH levels in MM [62], but had no relation with plasma cell%, vascular endothelial growth factor (VEGF), basic fibroblast growth factor (b-FGF), interleukin-1β (IL-1β), β2 microglobulin and C-reactive protein (CRP) [63]. Furthermore the leptin values may have increasing trend according to disease stage (Durie-Salmon criteria) [61, 63].

One study showed immunohistochemical staining for leptin receptor in bone marrow biopsies from 5 MM patients and detected the nuclear expressions of leptin receptor were in 2/5 cases [61]. OB-Rb mRNA expression of MM cell lines- ANBL-6 and RPMI 8226 cells was detected in another study. The receptor expression patterns were not altered after 24 hours culture with human recombinant leptin (100 ng/mL). Leptin stimulating changed gene expression profiles involved in cell survival, hematopoiesis, immune and lymphoid functions in the two myeloma cell lines, particularly in RPMI 8226 cells. And more importantly the expressions of B-cell receptor signaling related genes were altered [62].

A prospective study enrolled 155,000 individuals from ten U.S. cities and collected their blood samples to detected serum concentrations of adipokines. At the end of 8-year follow-up, 174 patients with an incident diagnosis of MM were identified. The researchers observed negative relation between adiponectin and MM risk. While leptin levels were found no association with the disease [64]. One retrospective case-control study reported similar results [65].

It seems that circulating leptin level is increased in ALL and MM patients, but not in NHL. The cytokine may be correlated with certain clinical parameters and increase proliferation of several malignant cell lines. Leptin receptor is expressed at relatively low level in most lymphoid neoplasms, except in NHL. Whereas the association between leptin receptor and disease prognosis remains inconsistent.

## Conclusion

Leptin/leptin receptor signaling has extensive physiological effects on metabolism, immunity, hematopoiesis, and so on. Leptin receptor expresses in blood cells of different developmental stages. In blast cells of hematologic malignancies, leptin exerts significant influence in cell proliferation and apoptosis through JAK/STAT, PI3K/AKT or MAPK signaling pathway. Serum leptin concentrations are enhanced in patients with certain hematologic neoplasms, such as ALL and MM. Furthermore the adipokine has correlation with clinical characters and treatments of patients with hematologic malignancies. All these findings emphasize the fact that leptin and its receptor included in the onset and progression of malignant blood disease and suggest leptin may be useful to detect disease progression and evaluate therapeutic response. Additionally, inhibition of this pathway may be a promising therapeutic approach.

Although recent important contributions have been made, more investigations should address the effects of leptin on hematologic diseases, and in particular, what role it plays in tumor microenvironment. Future studies should be conducted focusing on subgroups of leukemia and lymphoma. And more in vivo studies should be performed to elucidate the systematic action of leptin in the pathogenesis of malignant blood disease.

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## Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Xin Wang, Department of Hematology, Provincial Hospital Affiliated to Shandong University, 324 Jingwu Road, Jinan 250021, Shandong, China. Tel: 0086-531-68776358; 0086-13156012606; Fax: 0086-531-87068707; E-mail: xinw007@126.com

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