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Prognostic significance of serum survivin in Syrian childhood acute lymphoblastic leukemia

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is the highly usual childhood tumor. Survivin is a rare organ of the inhibitor of apoptosis protein family. Survivin was defined in different tumors and found to relate with lowly prognosis in a variation of cancers counting hematologic malignancies. The purpose of our study was to identify the prognostic importance of serum survivin levels in children with acute lymphoblastic leukemia. Our study included 24 children (15males, 9females) newly diagnosed who have acute lymphoblastic leukemia. Serum survivin levels were assayed by quantitative sandwich enzyme immunoassay (ELISA) before any therapy and at day 35 of induction therapy. Our results have presented an important decrease of serum survivin levels were observed in ALL patients after therapy (330 ± 221 pg/L) than in the same ALL patients before therapy (467.1 ± 246 pg/L). Our study proposes that we may use serum level of survivin as a marker of response to therapy in children with acute lymphoblastic leukemia.

KEY WORDS: Acute Lymphoblastic Leukemia, Survivin, ELISA, Therapy.

1. INTRODUCTION

Leukemia is a heterogeneous hematologic tumor creating from a multipotent hematopoietic stem cell (Kesy and Januszkiewicz-Lewandowska 2015). Acute lymphoblastic leukemia (ALL) is the highly usual childhood tumor, around 25% of totally childhood cancers (Ward, DeSantis, 2014). It is considered as the part of the first tumor that respond to chemotherapy and hence may be treated in a majority of children (Pui, 2000). However the general prognosis for patients who have ALL has improved throughout the gone periods, with a general survival of around 45%-60% for adults and around 80% for children, but reversion of drug-resistant leukemia persists a considerable problem (Park, Gang, 2011). At around 80% of pediatric patients who have ALL have B-precursor immunophenotype (Bp ALL), that includes a wide range of patients, including many of the lowest-risk patients with childhood ALL. Conversely, those with T-cell immunophenotype include about 10% to 15 % of pediatric ALL, and have traditionally been linked with a lower cure rate(Gaynon, Angiolillo, 2010). Nevertheless, identification of these patients and cure with more insistent regiments has led to survival rates that approach that of Bp ALL(Gaynon, Angiolillo, 2010), with the possible exception of early T-precursor (ETP) ALL, a particular subset of T-cell ALL that has been linked with a lower prognosis(Neumann, Vosberg, 2014). There are a growing amount of studies regarding the relationship among survivin and ALL (Yang, Liu, 2013).

Programmed cell death is a characteristic of living cells, and impaired cells are isolated in this system. Inhibitors of programmed cell death abnormally extend cell viability, so paying to the incidence and development of cancers (Esh and Atfy, 2011). Apoptosis may be prompted by two detached pathways: the intrinsic mitochondrial pathway and a death-receptor mediated extrinsic pathway. Both apoptotic pathways for caspase stimulation congregate on downstream effector caspases frequently result in activation of the effector caspases 3 and 7 (Altieri, 2003). Control of apoptosis is skillfully poised by signaling pathways between apoptosis-promoting agents such as p53 and caspases, and antiapoptotic agents such as Bcl-2 and MDM2 (Miyashita & Krajewski, 1994). Inhibitor of apoptosis proteins (IAP) is a key gene family responsible for apoptosis regulation. Steady with their capacity to stop the popular pathway of apoptosis, IAPs restrain multiple cell death incentives started by the extrinsic, i.e. death receptor, or intrinsic, i.e. mitochondrial, apoptotic pathways (Ward & DeSantis, 2014). Damaged apoptosis is interceded by parts of the inhibitor of apoptosis proteins (IAP) family for example survivin (Zhu & Gu, 2006). Survivin is a double functional protein that actions as a suppressor of apoptosis and works a central function in cell division (Zaffaroni 2007). Several studies in solid cancers have shown a relationship among survivin expression and a clinically disapproving sequence of disease, proposing that survivin expression is a weak prognostic feature (Esh and Atfy, 2011). Survivin was too exposed to play a task in the proliferation of leukemia which was prompted via inner tandem duplication of FLT3,17 and can stimulate tumorigenesis in vivo via pass on a survival benefit (Small & Keerthivasan, 2010). Very chemotherapeutic factors prompt cancer cell killing via apoptosis (Aref & Salama, 2004). Lowly answer to induction therapy or persistence of nominal remaining disease, that is accountable for the following relapse, can be produced via the challenge of leukemic blasts to stimulation of apoptosis (Aref and Salama, 2004). Furthermore, raised survivin expression in tumor has been connected with weak prognosis (Park and Gang, 2011). Survivin has been suggested as a smart aim for new antitumor intermediations (Sah and Khan, 2006).

In our study we investigated the role of serum survivin levels and evaluated survivin as a potential target for therapy of primary ALL.

2. METHODS AND MATERIALS

This study involved 24 patients (15males and 9 females) below 15 years, who were newly diagnosed with acute lymphoblastic leukemia (18 B cell and 6 T cell) and cured at Children University Hospital in Damascus in the period from 2015 to 2016. Leukemia was diagnosed and classified affording to the French–American–British (FAB) criteria. A written consent was acquired from parents of children. All patients received chemotherapy according to BFM 95 Protocol that consists of induction therapy, that consisted of 60 mg/m^2 oral prednisolone (PRD) for 4 weeks, 1.5 mg/m^2 intravenous (iv) VCR and 30 mg/m^2 iv DNR on days VIII, fifteenth, twenty tow, and twenty nine, and 5.000 iu/m^2 iv ASP on days twelve, fifteenth, eighteenth, twenty one, twenty four, twenty seven, thirtieth, and thirty-third.

Blood samples (5 to10ml) were taken from all patients into tubes without anticoagulant previous any therapy and at day 35 of induction therapy. Serum samples were separated and later kept at −80°C until subsequent processing and measurements.

Serum Survivin levels were measured using enzyme-linked immunosorbent assay (ELISA) kit manufactured by SunRed Company, China. The assay uses the quantitative sandwich enzyme immunoassay technique. The steps of kit were described by the manufacturer.

Statistical analysis: data was evaluated via SPSS (version21, IBM SPSS), and Microsoft Excel 2013. Quantitative variables were reported as mean ± standard deviation. Student's t test was performed to assess whether the results are significant or not. P<0.05 was reflected statistically important.

3. RESULTS

A significant reduction of serum levels of survivin were observed in ALL patients after therapy (330 ± 221 pg/L) than in the same ALL patients before therapy (467.1 ± 246 pg/L)

Table.1. Serum survivin (pg/L) in patients before and after therapy

	Number	Serum survivin (pg/L)
Before therapy	24	467.1 ± 246
After therapy	24	330 ± 221
P-value		<0.05

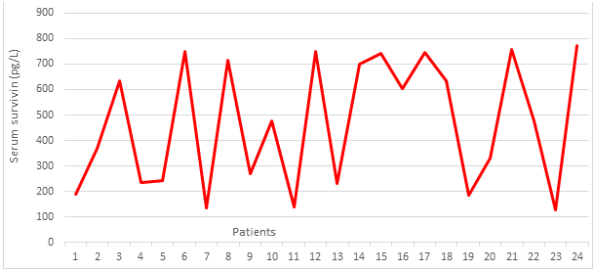

Figure.1. Serum levels of survivin (pg/L) in patients before therapy

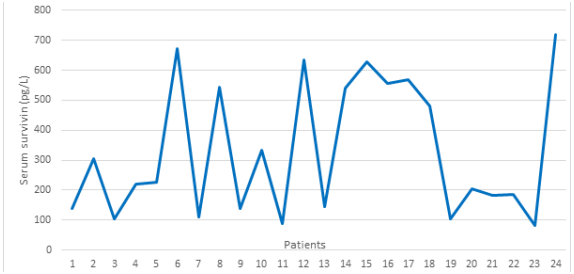

Figure.2. Serum levels of survivin (pg/L) in patients after therapy

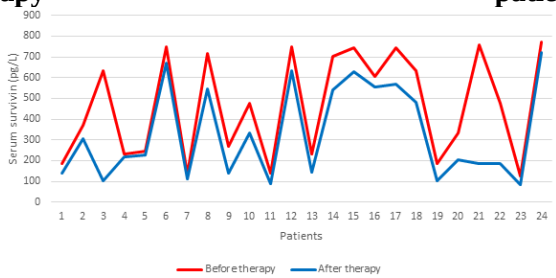

Figure.3. Serum survivin (pg/L) in patients before and after therapy

DISCUSSION

Our study of the few studies that measured levels of survivin in the serum in children with acute lymphoblastic leukemia by using monoclonal antibodies, since the majority of previous studies evaluated the expression of survivin in either frozen tissue or in paraffin-embedded materials. In our study, we have relied on the detection of the survivin levels in serum via ELISA, because of this method has advantages of being non-invasive and easy application.

Serum survivin levels were significantly greater in patients before therapy than after therapy. High serum survivin levels in patients before therapy can be defended via the lysis of circulating tumor cells and the release of their intracellular survivin or it might signify the perseverance of remaining cancer cells (Ahmed, Shehata, 2012). Very chemotherapeutic factors prompt tumor cell killing via apoptosis (Aref, Salama, 2004), and direct to decrease

of circulating tumor cells in acute lymphoblastic leukemia (Payne and Vora, 2007), and hence leads to reduction in serum survivin levels after therapy . Our results are supported by Man Yang, who confirmed that survivin/NF-κB signal transduction pathways could effect leukemia therapy, and after therapy, survivin expression reduced significantly in the HL60/adr cell line (Yang & Liu, 2013). Also there is confirmation that survivin acts a key function in the drug challenging phenotype of human tumor cells (Pennati & Folini, 2007). The Zhang (2005), study showed that large expression of wild-type survivin in human prostate tumor cell lines enlarged the challenge to taxol in vitro and in vivo (Zhang, Mukherjee, 2005). High degrees of survivin expression have been related to lowly prognosis and reduced survival ratios in patients who have solid tumors, acute leukemia, and lymphoma (Cong and Han 2004). Consequently, high serum survivin levels in patients after therapy are connected with treatment resistance and shortened patient survival, while low serum levels of survivin in patients after therapy are evidence of patient's compliance for therapy.

4. CONCLOSION

It may be useful following responses of patients with acute lymphoblastic leukemia by assaying serum survivin levels which considered as a therapeutic target.

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