Elmer Press

Short Communication

J Hematol • 2012;1(1):20-22

# BAFF Levels Are Elevated in Paediatric Patients With Acute Lymphoblastic Leukaemia Compared to Other B-Lineage Neoplasms

Julie Bienertova-Vasku[a,b,c,e], Petr Bienert[a], Daniela Kodytkova[b], Filip Zlamal[a], Josef Tomandl[d], Marie Tomandlova[d], Anna Vasku[a], Jaroslav Sterba[b]

## Abstract

There is emerging evidence that B-lineage neoplasms have aberrant expression of B-cell activating factor (BAFF) that enables the B cells to escape apoptosis. The aim of the study therefore was to investigate circulating levels of BAFF in paediatric malignancies related to B-cell growth, i.e. B-cell acute lymphoblastic leukaemia (B-ALL) and B-lineage lymphomas. We observed significant differences in circulating levels of BAFF between the B-ALL patients and B-cell lymphoma patients (Bcp-ALL: 7764 ± 6329 pg/ml, B-cell lymphoma: 2675 ± 1544 pg/ml; P = 0.0268), the circulating levels of BAFF being substantially higher in B-ALL cases.

**Keywords:** B-cell activating factor; Acute lymphoblastic leukaemia; B-cell lymphoma; Paediatric

## Introduction

There is emerging evidence that the TNF superfamily member B-cell activating factor (BAFF), along with its receptors, is a critical factor for growth and survival of both normal and malignant B clones of B cells [1]. BAFF, also known as BLyS,1 TALL-14 or THANK, is expressed as a type II transmembrane protein (biologically active 17 kDa molecule), and levels of BAFF are physiologically upregulated by interferon (INF)-c, interleukin (IL)-10 and CD40 ligand produced during inflammation and/or chronic infections [2].

It has been reported that BAFF can augment tumor cell growth of B-cells by either stimulating proliferation, inhibiting apoptosis or protecting malignant cells against drug-induced apoptosis [3]. In accordance with this, there is emerging evidence that B-lineage neoplasms have aberrant expression of BAFF [4]. As it was demonstrated that non-malignant B cells up-regulate BAFF upon stimulation by T cell CD40 ligand [5], it can be hypothesized that malignant B cells deregulate an otherwise physiological autocrine survival pathway to evade apoptosis. Thus, neutralization of BAFF signalling by receptors antagonists could be useful to dampen the accumulation of malignant B cells in B-lineage neoplasms patients and the blockage of the BAFF pathway could be suggested a plausible therapeutic strategy for oncology.

In addition to various autoimmune diseases and allergy, high BAFF levels were demonstrated in the serum of adult patients with B-cell chronic lymphocytic leukaemia CLL [3]. However, no study was published so far that would focus on BAFF levels in children with B-lineage neoplasms, such as acute lymphoblastic leukemias (ALL) and B-cell lymphomas. Therefore, the aim of our study was to investigate the pre-treatment BAFF levels in a cohort of children with B-cell neoplasms.

## Materials and Methods

This cross-sectional study includes the total of 18 children with B-lineage neoplasms (11 children with B-cell lymphoma, mean age at onset ± SD: 11.4 ± 4.8 y; 7 children with B-cell precursor ALL, mean age at onset ± SD: 6.1 ± 6.1 y) that were diagnosed at the Department of Paediatric Oncology of the University Affiliated Hospital Brno between January

Manuscript accepted for publication January 25, 2012

[a]Department of Pathological Physiology, Masaryk University, Kamenice 5, A18, 62500, Brno, Czech Republic
[b]Clinic of Paediatric Oncology, University affiliated Hospital Brno, Cernopolni 22, 612 00, Czech Republic
[c]Department of Laboratory Medicine, Masaryk Memorial Cancer Institute, Zluty kopec 7, 656 53, Brno, Czech Republic
[d]Department of Biochemistry, Masaryk University, Kamenice 5, A16, 625 00, Brno, Czech Republic
[e]Corresponding author: Julie Bienertova-Vasku, Department of Pathological Physiology, Masaryk University, Kamenice 5, A18, 625 00, Brno, Czech Republic. Email: jbienert@med.muni.cz

doi:10.4021/jh104e

and June 2011. All the sampling had been performed before the treatment was initiated according to respective protocols (Interim AIEOP BMF ALL 2000, Interim AIEOP BFM ALL 2009, Interfant 06, Interim AIEOP BFM 2011), blood samples for BAFF plasma analysis were collected after overnight fasting and were immediately centrifuged at 1700 g for 20 min and then stored at -80 ºC until analysis. Plasma BAFF levels were measured by commercially available ELISA (R&D Systems, Minneapolis, MN, USA).

## Results

We observed significant differences in circulating levels of BAFF between the B-ALL patients and B-cell lymphoma patients (Bcp-ALL: 7764 ± 6329 pg/ml, B-cell lymphoma: 2675 ± 1544 pg/ml; P = 0.0268), the circulating levels of BAFF being substantially higher in B-ALL cases than in B-cell lymphoma cases.

### B-ALLs

No association of BAFF levels with the white blood count at the time of diagnosis or at day 8 or 33 was observed; moreover we observed no association with cytogenetic phenotype of the leukemia. Surprisingly, in the B-ALL patients, the BAFF reached an extreme level in the only child classified as a high-risk ALL (more than 10 000 pg/ml).

### B-cell lymphomas

When analyzing the B-cell lymphomas separately, we observed no differences in BAFF levels between the patients with Hodgkin and non-Hodgkin lymphomas (Hodgkin: 2443 ± 1598 pg/ml, non-Hodgkin: 2868 ± 1621 pg/ml; P = 0.7922).

As there was a significant difference in age between the B-ALL and B-cell lymphoma patients, we employed a regression model to analyse whether there was an association between BAFF levels and the age of the infant. However, no correlation was observed between BAFF level and age of the child (r = -0.06, P = 0.81).

## Discussion

Previous studies reported that BAFF is directly involved in regulation of development and homeostasis of B-cells after their exit from the bone marrow, whereas the B-cell primarily imigrate to the spleen as early transitional (T1) B cells [5]. Selection and maturation of transitional B cells continues in the periphery leading to development of follicular (Fo B) 6 and marginal zone (MZ) B cells likely via late transitional T2-follicular (CD21int-T2) precursor stage [6]. Peripheral differentiation is accompanied by increasing resistance to passive or BCR-induced apoptosis [7]. As the T1 cells are more sensitive with respect to BCR cross-linking [8], they are likely to be selected through a process of negative selection, which should lead to removal of self-reactive B-cells [5]. However, B cells can reach survival advantage during positive selection by becoming responsive to BAFF [5] and recent studies show that CD21int-T2 B cells express higher levels of BAFF-R [8] and display enhanced responsiveness to BAFF relative to T1 B cells, which is in accordance with the previous reports of dysregulated BAFF levels in T2 diseases. It has been reported recently [5] that gain of survival potential within transitional B cells is dependent on the ability to produce a long-term c-Rel response, which plays a critical role in T2 B cell survival and differentiation in vivo by further inducing anti-apoptotic genes, BAFF-R and NF-κB2, an essential component for BAFF-R survival signalling. The anti-apoptotic trend in the T2 B cells mediated via BAFF pathway could also provide an elegant explanation for observed connections between autoimmunity and cancer, e.g. the higher prevalence of lymphomas in patients with autoimmunity.

Our study presents a small piece of puzzle of understanding BAFF involvement in B-lineage neoplasms as it provides an important application of conclusions made by Mihalcik et al [8] on the B-ALL cell lines in vitro for B-ALL patients *in vivo*. Although highly limited in number, our study provides a potential basis for further evaluation of BAFF as a diagnostic and/or prognostic marker in B-ALL, also with respect to initial staging of the disease, where elevated BAFF levels could play a role of a possible negative prognostic marker.

## Acknowledgement

The present study was supported by the projects MZ-MOU2005 and RECAMO CZ.1.05/2.1.00/03.0101.

## References

1. Moore PA, Belvedere O, Orr A, Pieri K, LaFleur DW, Feng P, Soppet D, et al. BLyS: member of the tumor necrosis factor family and B lymphocyte stimulator. Science. 1999;285(5425):260-263.
2. Morimoto S, Nakano S, Watanabe T, Tamayama Y, Mitsuo A, Nakiri Y, Suzuki J, et al. Expression of B-cell activating factor of the tumour necrosis factor family (BAFF) in T cells in active systemic lupus erythematosus: the role of BAFF in T cell-dependent B cell pathogenic autoantibody production. Rheumatology (Oxford). 2007;46(7):1083-1086.
3. Lied GA, Berstad A. Functional and clinical aspects of

the B-cell-activating factor (BAFF): a narrative review. Scand J Immunol. 2011;73(1):1-7.
4. He B, Chadburn A, Jou E, Schattner EJ, Knowles DM, Cerutti A. Lymphoma B cells evade apoptosis through the TNF family members BAFF/BLyS and APRIL. J Immunol. 2004;172(5):3268-3279.
5. Castro I, Wright JA, Damdinsuren B, Hoek KL, Carlesso G, Shinners NP, Gerstein RM, et al. B cell receptor-mediated sustained c-Rel activation facilitates late transitional B cell survival through control of B cell activating factor receptor and NF-kappaB2. J Immunol. 2009;182(12):7729-7737.
6. Meyer-Bahlburg A, Andrews SF, Yu KO, Porcelli SA, Rawlings DJ. Characterization of a late transitional B cell population highly sensitive to BAFF-mediated homeostatic proliferation. J Exp Med. 2008;205(1):155-168.
7. Su TT, Guo B, Wei B, Braun J, Rawlings DJ. Signaling in transitional type 2 B cells is critical for peripheral B-cell development. Immunol Rev. 2004;197:161-178.
8. Mihalcik SA, Tschumper RC, Jelinek DF. Transcriptional and post-transcriptional mechanisms of BAFF-receptor dysregulation in human B lineage malignancies. Cell Cycle. 2010;9(24):4884-4892.