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BIM is a prognostic biomarker for early prednisolone response in pediatric acute lymphoblastic leukemia

Nan Jiang[a], Grace Shimin Koh[a], Joshua Yew Lim[a], Shirley Kow Kham[a], Hany Ariffin[b], Fook Tim Chew[c], and Allen Eng Yeoh[d,e]

[a]*Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore;* [b]*Department of Paediatrics, University of Malaya, Kuala Lumpur, Malaysia;* [c]*Department of Biological Sciences, Faculty of Science, National University of Singapore, Allergy and Molecular Immunology Laboratory, Lee Hiok Kwee Functional Genomics Laboratories, Singapore;* [d]*Department of Paediatrics, Division of Haematology and Oncology, Yong Loo Lin School of Medicine, National University Health System, National University Hospital, Singapore;* [e]*Viva-University Children's Cancer Centre, University Children's Medical Institute and National University Cancer Institute, National University Health System, Singapore, Singapore*

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Objective. **Glucocorticoids such as prednisolone (PRED) are widely used in the treatment of pediatric acute lymphoblastic leukemia. In PRED-induced apoptosis, Bcl-2 family members play important regulatory roles. However, the exact members involved remain unknown. In this study, the roles of Bcl-2 family members in PRED-induced apoptosis and their prognostic value to day 8 PRED response are evaluated.**

Materials and Methods. **Four clinically important acute lymphoblastic leukemia cell lines, three PRED-sensitive (697, Sup-B15, and RS4;11) and one PRED-resistant (REH) were studied. Thirty paired patient bone marrow samples were obtained at diagnosis (day 0) and after 7 days (day 8) of PRED monotherapy. Twenty-five patients had PRED good response and five PRED poor response. Differential expressions of Bcl-2 members were observed in those samples and BIM was further investigated using gene silencing technology in representative cell line Sup-B15.**

Results. **The proapoptotic BH3-only Bcl-2 family member BIM was upregulated only in PRED-sensitive cells. Receiver operating characteristic curve analysis showed that BIM expression was highly predictive of PRED response (area under the curve = 0.81; $p = 0.032$) in paired patient bone marrow samples and is, most excitingly, independent of molecular subtype. Patients whose BIM protein expression levels fail to upregulate at day 8 compared to day 0 (D8/D0 ratio <0.93) have significantly poorer event-free survival (60%) than those patients whose BIM protein expression levels did upregulate (92%). By silencing BIM in PRED-sensitive cells, PRED-induced apoptosis was inhibited.**

Conclusions. **Upregulation of BIM by PRED in acute lymphoblastic leukemia cells regardless of molecular subtype is significantly prognostic of outcomes, confirming BIM's essential regulatory role in the PRED-induced apoptosis.** © **2011 ISEH - Society for Hematology and Stem Cells. Published by Elsevier Inc.**

Acute lymphoblastic leukemia (ALL) is a cancer of lymphoid progenitors, and most commonly affect children between the ages of 2 and 5 years [1]. It is characterized by abnormal accumulation of immature lymphocytes in the bone marrow [2]. Clinically, the response to initial treatment of prednisolone (PRED) is critically prognostic [3,4]. PRED, a glucocorticoid (GC), is used as the first drug in induction therapy due to its powerful apoptotic effect on ALL cells. Patients with $<1000/\mu L$ peripheral blast after 7 days of PRED (PRED good responders [PGR]) have significantly better outcomes than patients whose peripheral blast count is $>1000/\mu L$ (PRED poor responders [PPR]). In our Ma-Spore-ALL 2003 study carried out by Malaysia-Singapore Study Group (n = 472), we observed significantly lower event-free survival (EFS) in PPR (n = 50, EFS = 70.6%) when compared to PGR patients (n = 422, EFS = 83.7%)

Offprint requests to: Allen Eng Juh Yeoh, M.D., Department of Paediatrics, Division of Haematology and Oncology, Yong Loo Lin School of Medicine, National University Health System, Singapore, c/o Level 4, Main Building, National University Hospital, 5, Lower Kent Ridge Road 119074, Singapore; E-mail: allen.yeoh@nus.edu.sg

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