Respons steroid sebagai faktor prognostik kesintasan leukemia limfoblastik akut pada anak : tinjauan khusus pada penilaian imunofenotiping, sitogenetik, molekular, dan minimal residual disease = Steroid response as prognostic factor in survival of childhood acute lymphoblastic leukemia focus on immunophenotyping, cytogenetic, molecular, and minimal residual disease assessments

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Abstrak

Latar Belakang: Angka kesintasan LLA pada anak di negara berkembang masih tertinggal dibanding negara maju. Ketepatan diagnosis dan stratifikasi risiko pasien LLA merupakan hal penting yang perlu dievaluasi sebagai langkah awal untuk meningkatkan kesintasan. Di negara maju ketepatan diagnosis dan stratifikasi risiko didasarkan atas hasil pemeriksaan morfologi, imunofenotiping, sitogenetik, dan molekular. Di Indonesia, hal tersebut belum dapat dilakukan sepenuhnya karena keterbatasan biaya dan fasilitas. Untuk itu, perlu kriteria stratifikasi berdasarkan klinis dan laboratorium sederhana tetapi mampu mendekati stratifikasi molekular. Respons steroid merupakan faktor prognostik kuat dalam memprediksi kejadian relaps dan memengaruhi angka kesintasan. Penambahan variabel respons steroid pada stratifikasi RSCM (stratifikasi modifikasi) diharapkan dapat mendekati kemampuan stratifikasi molekular sebagai baku emas.
Metode: Penelitian kohort prospektif selama 6 bulan dilakukan di Departemen Ilmu Kesehatan Anak FKUI-RSCM pada Januari 2013 - September 2014. Subjek adalah pasien baru terdiagnosis LLA kemudian dikelompokkan menjadi risiko biasa(RB) dan risiko tinggi (RT) berdasarkan kriteria stratifikasi RSCM (usia, jumlah leukosit, massa mediastinum dan infiltrasi SSP). Subjek dengan RB mendapat prednison (60 mg/kgBB/hari) dan RT mendapat deksametason (6 mg/kgBB/hari) selama 7 hari. Respons steroid dievaluasi pada hari ke-8, dengan menghitung blas di darah tepi. Respons baik bila jumlah blas < 1.000/L dan respons buruk bila jumlah blas > 1.000/L. Subjek dengan respons buruk dikelompokkan RT sesuai stratifikasi risiko yang baru (stratifikasi modifikasi). Evaluasi remisi fase induksi dilakukan setelah 6 minggu pemberian kemoterapi berdasarkan persentase blas dan minimal residual disease (MRD) sumsum tulang. Kriteria risiko tinggi pada stratifikasi molekular bila terdapat fusi gen E2A-PBX1, MLL-AF4, dan BCR-ABL, sedangkan risiko biasa bila terdapat fusi gen TEL-AML1.
Hasil Penelitian: Pada penelitian ini diikutsertakan 73 subjek dengan rerata usia subjek 5,5 (SB ± 3,8) tahun. Subjek lelaki (65,8%) lebih banyak dibanding perempuan (34,2%). Gejala klinis yang sering ditemukan adalah pucat sebanyak 65 (89%), demam 53 (72,6%), nyeri tulang 51 (70%), dan hepatomegali 51 (70%) subjek. Hasil pemeriksaan imunofenotiping mendapatkan 77,1% sel B, 17,1% sel T, dan 5,7% sel campuran. Ketidaksesuaian remisi fase induksi berdasarkan morfologi dan MRD sebesar 15,2%. Stratifikasi RSCM maupun modifikasi tidak berkorelasi dengan stratifikasi molekular (r = 1,1; p = 0,6). Angka kesintasan berdasarkan stratifikasi molekular (79%) lebih tinggi dibandingkan stratifikasi RSCM (68,5%) maupun modifikasi (69,6%).
Simpulan: Stratifikasi modifikasi menunjukkan kemampuan yang sama dengan stratifikasi RSCM dibandingkan stratifikasi molekular. Angka kesintasan berdasarkan stratifikasi molekular lebih tinggi dibandingkan stratifikasi RSCM dan modifikasi.

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Introduction: Survival rate of children with ALL in developing countries remains lower compared to developed countries. Diagnosis and risk stratification are important to determine survival rates. Diagnosis and risk stratification in developed countries are based on morphology, immunophenotyping, cytogenetic, and molecular examination of bone marrow while in Indonesia most of those examinations are not available due to financial and facilities limitation. Therefore, we need to develop stratification criteria based on clinical and laboratory assessment which is comparable to molecular stratification. Response to steroid is a strong predictor of relapse and survival rates in ALL. The aim of the study is to develop new stratification to improve accuracy in predicting relapse rate and increase survival rate, by adding steroid response variable to current CMH stratification, in comparison with molecular stratification as gold standard.

Methods: A prospective study was conducted at Pediatric Hematology-Oncology Division, Department of Child Health, FMUI-CMH on January 2013 - September 2014. Morphology, immunophenotyping, cytogenetic and molecular assessment were performed. Patient was stratified into standard risk (SR) and high risk (HR) based on CMH stratification criteria (based on age, WBC, mediastinal mass and CNS infiltration) and given steroid (prednisone or dexamethasone) for 7 days. Steroid response was evaluated at day 8, good response if peripheral blast count < 1,000/L and poor response if > 1,000/L. Poor responders were moved to HR group in new stratification (modified stratification). Bone marrow aspiration and minimal residual disease (MRD) detection were perfomed after induction phase to evaluate remission and patient was observed for 6 months. High risk criteria based on molecular stratification are E2A-PBX1, MLL-AF4 and BCR-ABL fusion genes, while standard risk is TEL-AML1.

Results: A total of 73 newly diagnosed ALL patients were enrolled in this study. The mean age was 5.5 (SD ± 3.8) years. Incidence in male (65.8%) is higher than female (34.2%). Clinical characteristics are pale (89%), fever (72.6%), bone pain (70%), hepatomegaly (70%), bleeding (42.5%), lymphadenopathy (49.0%), and splenomegaly (46.6%). Immunophenotyping result was 77.1% for B-lineage; 17.1% T-lineage; and 5.7% mixed lineage. Minimal residual disease detection from 33 patients showed no difference in remission between CMH and modified stratification. Four patients were moved to HR after evaluation of steroid response. We found discrepancy of remission induction results based on morphology and MRD in 15.2% subjects. Survival rate for CMH, modified, and molecular stratification were 68.5%, 69.6%, and 75.5%, respectively. Cipto Mangunkusumo Hospital and modified stratification were not correlated with molecular stratification as the gold standard ($r = 1.1$; $p = 0.6$).

Conclusions: Modified stratification had similar accuracy with CMH stratification compare to molecular stratification in predicting survival rate of ALL children. Remission based on MRD detection between the two stratification was also similar. Survival rate by molecular stratification was higher compared to CMH or modified stratification.