Toksisitas Hematologi pada Leukemia Limfoblastik Akut Anak yang Mendapat Terapi Fase Pemeliharaan: Kajian Khusus Terhadap Genotip dan Fenotip Metabolisme Merkaptopurin = Hematotoxicity in Acute Lymphoblastic Leukemia Children during Maintenance Therapy: Focussed on Genotyping and Phenotyping on Mercaptopurine Metabolism

Dewi Selvina Rosdiana, author

Abstrak

Hematotoksisitas pada leukemia limfoblastik akut (LLA) anak selama terapi fase pemeliharaan, merupakan hal penting, karena dapat menyebabkan kondisi mengancam jiwa dan penghentian dini terapi, yang dapat meningkatkan risiko relaps. Untuk menghindari hematotoksisitas, American Society for Clinical Pharmacology and Therapeutics merekomendasikan penyesuaian dosis awal merkaptopurin (6MP) berdasarkan genotip enzim pemetabolisme 6MP yaitu thiopurine S-methyl transferase (TPMT), berdasarkan studi-studi sebelumnya polimorfisme enzim tersebut memengaruhi kadar metabolit aktif 6MP dan hematotoksisitas.

Penelitian ini bertujuan untuk mengetahui prevalensi hematotoksisitas dan melihat hubungannya dengan genotip TPMT, fenotip TPMT, dan karakteristik pada pasien LLA anak di Indonesia. Studi potong lintang dilakukan di RS Cipto Mangunkusumo dan RS Kanker Dharmais pada bulan Juni 2017–Oktober 2018 terhadap 106 pasien LLA anak yang sedang mendapatkan 6MP minimal 1 bulan pada terapi fase pemeliharaan.

Prevalensi hematotoksisitas pada fase pemeliharaan pasien LLA anak di Indonesia 71,7%, dengan neutropenia 51,9%, anemia 44,3%, dan trombositopenia 6,6%. Neutropenia tingkat 3–4 sebesar 9,4%. Alel mutan yang ditemukan hanya TPMT*3C dengan frekuensi 0,95%. Kadar 6TGN, 6MeMP dan rasio kadar 6MeMP/6TGN sangat bervariasi, yaitu 6–234,04 pmol/8x10⁸ eritrosit, 3,5–3167,01 pmol/8x10⁸ eritrosit, dan 0,06–100,64 pmol/8x10⁸eritrosit, secara berurutan. Sebesar 76,4% pasien berusia antara 1–10 tahun dan > 95% pasien memiliki status gizi dan kadar albumin normal. Proporsi pasien berdasarkan stratifikasi risiko dan dosis harian 6MP sebanding. Tidak terdapat hubungan antara hematotoksisitas dengan genotip TPMT, usia, status gizi, kadar albumin, stratifikasi risiko, cara pemberian dosis harian 6MP, dan pemberian bersama kotrimoksazol. Faktor yang berhubungan dengan hematotoksisitas adalah fenotip TPMT: kadar 6MeMP (p = 0,004) dan rasio kadar 6MeMP/6TGN (p = 0,010). IMT 16,6 kg/m2 berhubungan dengan anemia dan kadar albumin serum 4,2 g/dL berhubungan dengan trombositopenia. Tidak terdapat hubungan antara genotip dengan fenotip TPMT pada pasien LLA anak di Indonesia.

Kesimpulan: Hematotoksisitas tidak berhubungan dengan genotip TPMT dan karakteristik pasien. Fenotip TPMT berhubungan dengan hematotoksisitas, namun kurang kuat untuk memprediksi hematotoksisitas.

.....Hematotoxicity in acute lymphoblastic leukemia (ALL) children during maintenance phase therapy is important, because it can cause life-threatening conditions and it is the major cause of drug discontinuation, which can increase the risk of relapse. To reduce hematotoxicity, American Society for Clinical Pharmacology and Therapeutics recommended to adjust starting dose of mercaptopurine (6MP) based on

patient's genotype of thiopurine S-methyl transferase (TPMT), that affected 6MP active metabolite levels and hematotoxicity.

The aim of the study was to determine the prevalence of hematotoxicity and factors that affecting hematotoxicity, focus on genotype and phenotype of TPMT. A cross-sectional study was conducted at Cipto Mangunkusumo Hospital and Dharmais Cancer Hospital in June 2017–October 2018 for 106 LLA patients who were receiving at least 1 month of 6MP during maintenance therapy.

The prevalence of neutropenia, anemia, and thrombocytopenia were 51.9%, 44.3%, and 6.6%, respectively. We found only TPMT *3C with a frequency of 0.95%. Erythrocyte levels of 6TGN, 6MeMP, and ratio of 6MeMP/6TGN levels vary greatly, 6–234,04 pmol/8x10⁸ RBC, 3,5–3167,01 pmol/8x10⁸ RBC, and 0,06–100,64 pmol/8x10⁸ RBC. About 76.4% of patients aged 1–10 years, and > 95% of patients had normal nutritional status and serum albumin levels. The proportion of patients based on risk stratification and daily dose of 6MP were comparable. There was no association between hematotoxicity and genotype TPMT, age, nutritional status, serum albumin levels, risk stratification, daily dose of 6MP, and co-administration of cotrimoxazole. The factor associated with hematotoxicity was the TPMT phenotype: 6MeMP levels ($p = 0.004$) and the ratio of 6MeMP/6TGN levels ($p = 0.010$). BMI 16.6 kg/m2 was associated with anemia and serum albumin level 4.2 g/dL was associated with thrombocytopenia. There was no relationship between genotype and the TPMT phenotype in pediatric LLA patients in Indonesia.

Conclusion: Hematotoxicity is not associated with TPMT genotype and patient characteristics. The TPMT phenotype is associated with hematotoxicity but is not strong enough at predicting hematotoxicity.