Respons Terapi Fase Induksi Leukemia Mieloblastik Akut Pada Anak: Tinjauan Khusus Pada Ekspresi Cd7, Cd19, T(8;21), Inv(16), Mutasi Flt3-Itd Dan Mutasi Npm1 = Pediatric Acute Myeloid Leukemia Induction Phase Response: Focus on CD7 and CD19 aberrants, t(8;21) and inv(16) karyotypes, FLT3-ITD and NPM1 Mutations

Hikari Ambara Sjakti, author

Abstrak

Pasien leukemia mieloblastik akut (LMA) yang mencapai remisi komplet pascaterapi induksi di Indonesia hanya 49%, dan event-free survival (EFS) hanya 10%. Angka kekambuhan dan kematian terkait kemoterapi menjadi penyebab rendahnya luaran tersebut. Untuk meningkatkan luaran dan mengurangi efek samping pengobatan perlu dilakukan stratifikasi risiko menggunakan profil sitogenetik maupun imunofenotipe. Tujuan penelitian ini adalah mendapatkan profil imunofenotipe, kariotipe, mutasi FLT3-ITD dan NPM1 (variabel prognosis), serta hubungannya dengan respons kemoterapi induksi.
Penelitian dilakukan dengan desain kohort analitik pada LMA usia 1–18 tahun di RSCM, RSABHK, RSKAD, RSPAD pada bulan November 2018 hingga Maret 2020. Pemeriksaan yang dilakukan meliputi ekspresi CD7, CD19, kariotipe t(8,21), inv(16), mutasi NPM1 dan FLT3-ITD, kemudian dinilai hubungannya dengan kejadian remisi setelah mendapat terapi induksi dengan protokol LMA Nasional.
Dari 42 subjek diperoleh median usia 8 tahun 11 bulan (3–213 bulan). Tipe LMA terbanyak adalah M1, diikuti M2. Gejala klinis tersering pucat (33/42) dan demam (25/42). Tanda klinis terbanyak hepatomegali (17/42) dan splenomegali (18/42). Subjek dengan CD7+ 21,4%, CD19+ 11,9%. Translokasi t(8;21) terdeteksi pada 1dari 18 (5,6%) subjek, inv(16) pada 4 dari 18 ((22%) subjek, 7 dari 18 subjek termasuk kelompok kariotipe favorable. Sebanyak 2 dari 28 (7%) subjek memiliki mutasi FLT3-ITD. Mutasi NPM1 tidak ditemukan. Ekspresi CD7 lebih dominan berperan dibandingkan usia dan jumlah leukosit saat diagnosis sebagai faktor prognosis baik. Analisis multivariat menunjukkan hubungan bermakna antara variabel prognosis dengan respons terapi induksi. Aberans CD7, inv(16) dan mutasi FLT3-ITD memiliki risiko relatif lebih tinggi untuk remisi (masing-masing incidence rate ratio/IRR 3,39 (IK 95% 1,43–8,04); IRR 2,36 (IK 95% 1,08–5,17); dan IRR 4,08 (IK 95% 1,78–9,34)). Nilai IRR aberans CD19 dan t(8;21) IRR < 1.
Penelitian ini menunjukkan aberans CD7, inv(16) dan mutasi FLT3-ITD dapat dijadikan faktor prognosis baik sedangkan aberans CD19, kariotipe t(8;21) dapat dijadikan faktor prognosis buruk pada LMA anak di Indonesia.
.....Currently, pediatric acute myeloid leukemia (AML) patients who achieved complete remission after induction therapy has reach only 49% with 10% event-free survival (EFS) rate. The relapse rate and mortality related to chemotherapy are the causes of this low outcome. To improve outcomes and reduce side effects of treatment, it is necessary to carry out risk stratification using cytogenetic profiles and immunophenotypes. The purpose of this study was to obtain profiles of immunophenotype, karyotype, FLT3-ITD and NPM1 mutations (prognostic variables), and their relationship to the response to induction chemotherapy.
The study was conducted with an analytical cohort design on AML patients aged 1–18 years at RSCM,

RSABHK, RSKAD, RSPAD from November 2018 to March 2020. The examinations included expression of CD7, CD19, karyotype t(8.21), inv(16), NPM1 and FLT3-ITD mutations, then assessed the relationship with the incidence of remission after receiving induction therapy with the National AML protocol.
Of the 42 subjects, the median age was 8 years 11 months (3–213 months). The most common type of AML was M1, followed by M2. The most common clinical symptoms were pallor (33/42) and fever (25/42). The most common clinical signs were hepatomegaly (17/42) and splenomegaly (18/42). Subjects with CD7+ 21.4%, CD19+ 11.9%. Translocation t(8;21) was detected in 1 of 18 (5.6%) subjects, inv(16) in 4 of 18 ((22%) subjects, 7 of 18 subjects included in the favorable karyotype group. A total of 2 of 28 (7%) subjects had FLT3-ITD mutations. NPM1 mutation was not found. Role of CD7 expression as prognostic factor was more dominant than age and leukocyte count at diagnosis. Multivariate analysis using generalized linear model showed a significant relationship between prognostic variables and response to induction therapy. CD7 aberrant, inv(16) and FLT3-ITD mutations had a higher relative risk for remission (respectively incidence rate ratio /IRR 3.39 (95% CI 1.43–8.04); IRR 2.36 (95% CI 1.08–5.17); and IRR 4.08 (95% CI 1.78–9.34)). Incidence rate ratio value of CD19 aberrant and t(8;21) IRR < 1.
This study showed that CD7 aberrant, inv(16) and FLT3-ITD mutations can be used as good prognostic factors, while CD19 aberrant, t(8;21) karyotype can be used as poor prognostic factors for pediatric AML in Indonesia.