refratário novamente. Para avaliação da resistência, foi solicitado cariótipo para avaliação de evolução clonal e a pesquisa de mutações genéticas de ponto no gene BCR-ABL. Esta foi confirmada pela presença de mutação na porção E459K, localizada no Activation-loop (A-loop) do domínio quinase da proteína ABL, o que dificulta a ligação do Imatinibe ao sítio catalítico e mantém a proteína ativada e em seu estado oncogênico. O mesmo mecanismo provavelmente ocorre para o Nilotinibe. O Ponatinibe, por sua vez, tem demonstrado eficácia contra mutações que afetam o A-loop, sendo assim a nova droga de escolha. **Conclusão:** Dessa forma, devido a possibilidade de resistência ao tratamento de primeira linha e também de segunda linha, temos a necessidade de opções como o Ponatinibe para o tratamento desses pacientes. Cabe ainda ressaltar a necessidade de novas drogas que consigam superar a possível resistência ao tratamento da LMC.

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IMMUNOLOGICAL PROFILES OF CYTOTOXIC CELLS IS ASSOCIATED WITH TREATMENT-FREE REMISSION IN CHRONIC MYELOID LEUKEMIA

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Patients with Chronic Myeloid Leukemia (CML) who achieve sustained deep molecular response (DMR) to Tyrosine Kinase Inhibitors (TKIs) are eligible for treatment discontinuation, but only 50% of those achieve long-term treatment-free remission (TFR). Current biomarkers that predict resistance to TKIs as well as loss of the molecular response after TKI interruption have not been defined. We hypothesized that antitumoral immunity mediated by Natural Killer (NK) and T cells may contribute to TFR success and result in distinct responses during treatment and after discontinuation. NK and T cells phenotype were correlated with *BCR::ABL1* kinetics and TFR success in a cohort of CML Brazilian patients included in the DES-CML study (Study of treatment discontinuation in CML treated at the Unified Health System), multicenter, prospective, open-label, single-arm, phase 2, non-randomized, ongoing trial, with current data from two Brazilian centers. Using flow cytometry, we evaluated frequency, subtypes, maturation, and receptors expression of NK and T cells from diagnosis to TKI discontinuation. Peripheral blood samples from 20 healthy controls and 68 CML patients were analyzed at different time points: 14 diagnosis (DX), 13 Imatinib failure (F), 7 major molecular response (MMR), 9 DMR, 20 TFR and 5 TFR loss (TFRL). Patients in discontinuation cohort had TKI dose reduced to 50% for 6 months before total suspension. NK cell subtypes were defined as secretory ($CD56^{bright}CD16^{-}$) or cytotoxic ($CD56^{dim}CD16^{+}$). We assessed NK maturation markers (CD57 and NKp80), activation (NKG2D,NKp46,DNAM-1), and inhibition receptors (KIR2DL1,TIGIT,NKG2A). PD-1 checkpoint inhibitor was assessed in CD8 T cells. The frequencies of cytotoxic ($p < 0.05$) and mature ($CD57^{+}$ and NKp80 $p < 0.05$) NK cells as well as NKG2D and DNAM-1 ($p < 0.05$) were lower in the DX, F, and TFRL groups as compared to patients under TKI treatment with DMR, TFR, and healthy individuals. Patients in TFR exhibited a distinct immune profile from TFRL patients that were not influenced by gender, TKI drug, ELTS or SOKAL score. TFR patients presented higher frequency of cytotoxic ($p < 0.05$) and mature ($CD57^{+}$ $p < 0.05$) NK cells, and also NKG2D, DNAM-1,NKp46 ($p < 0.05$) compared with TFRL. Frequency of PD-1 ($p < 0.05$) in T cells was decreased in TFR. At the TKI dose reduction timepoint,TFRL patients already had decreased frequency of cytotoxic ($p < 0.05$) and mature ($CD57^{+}$ $p < 0.05$) NK cells as well as of the activating receptor NKG2D ($p < 0.05$) compared with TFR cases. Conversely, T-cell PD-1 ($p < 0.05$) expression was higher in TFRL than in TFR patients at the dose reduction point. In conclusion, our study indicates that impaired NK cell function and PD-1 T-cell inhibition are major contributors to molecular responses in CML. Patients with sustained TFR exhibit higher frequencies of cytotoxic, mature and activated NK cells, along with lower PD-1 expression in T cells. These profile contrasts with patients who have persistent disease or lose molecular response post-treatment suspension, who demonstrate impaired NK cell function and increased PD-1 expression. Monitoring parameters such as mature NK content and activating receptors, particularly NKG2D, and PD-1 expression during the de-escalation phase of TKI potentially predicts TFR relapse and can be useful for decision-making in TKI interruption.

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GENE AND METABOLITE SIGNATURES IN CHRONIC MYELOID LEUKEMIA PROGRESSION: IMPLICATIONS FOR THERAPEUTIC RESISTANCE AND BIOMARKER DISCOVERY

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