CD8+ T cells, reinforcing immune immaturity. Frequencies of mature and cytotoxic NK cells (CD56dim, CD57+, NKp80), as well as NKG2D and DNAM-1, were lower in DX, F, and TFRL groups compared to DMR100, TFR, and healthy controls. PD-1 and CTLA-4 expression on CD8+ T cells was more pronounced in these groups. No significant differences were found in KIR2DL1 and NKG2A on NK cells or CD3, CD4, CD8 expression on T cells. **Discussion and conclusion:** These findings suggest that maturation and activation of cytotoxic compartments are crucial for disease control and TFR success. In contrast, immature and exhausted immune profiles may predispose to relapse. Immune dysregulation precedes molecular relapse, reinforcing the role of longitudinal immune monitoring. Progressive loss of mature NK cells and increased checkpoint expression may define an immunological risk profile for TFR failure. Immune assessment during dose reduction could guide clinical decisions on TKI cessation and support individualized strategies in CML based on immunological profiles.

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IMMUNE SENESCENCE AND EXHAUSTION PHENOTYPE MARKED BY LOSS OF NKG2D AND DNAM-1 NK ACTIVATING SIGNALING AND INCREASED TIM-3 T CD8 CHARACTERIZES ADVANCED MYELOFIBROSIS

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Introduction: Myelofibrosis (MF), driven by JAK/STAT signaling mutations in hematopoietic stem cells, has the worst prognosis among myeloproliferative neoplasms (MPNs), progressing from pre-fibrotic MF (PFMF) to overt MF (OMF). Although additional mutations promote clonal expansion, progression cannot be fully explained by clinical- mutational scores. Exposure to the leukemic inflammatory microenvironment may impair immune surveillance by cytotoxic cells such as Natural Killer (NK) and T lymphocytes, fostering disease advancement. **Objectives:** To investigate immune dysfunction across clinical and molecular MF subtypes, focusing on NK and T lymphocyte phenotype, maturation, and receptor expression, and to examine the leukemic microenvironment effects using a JAK2V617F murine model. **Material and methods:** We performed immunophenotyping of NK and T cells (frequency, maturation, and activation/inhibitory receptors) in peripheral blood mononuclear cells from untreated MF patients (13 PFMF, 16 OMF; 13 JAK2 wild-type, 18 JAK2-mutated) admitted at Ribeirao Preto Clinical Hospital (August 2022 – December 2024), and from age-matched healthy donors. To further explore the effects of soluble factors from the leukemic microenvironment, we established a chimeric murine model of JAK2V617F- driven MPN. Healthy recipient mice were transplanted with total bone marrow from JAK2V617F donor mice following sublethal irradiation (n = 4 MPN-exposed, 6 control- exposed). Four weeks post-transplant, spleen cells were collected, and NK and T cells were immunophenotyped. **Results:** MF patients exhibited increased frequencies of NK cells (CD45hiCD3-CD19-CD56+) compared to healthy donors, particularly CD56bright and immature subsets (CD27-CD11b-, CD27+CD11b-), and reduced frequencies of CD56dim, cytotoxic (CD27-CD11b+), and hypermature (CD57+NKp80+) NK cells. There was a decrease of NKG2A (total, cytotoxic, and hypermature NK cells) and NKp46 (total and hypermature NK cells) receptors. T cell maturation was also impaired, with reduced frequencies of stem central memory (CD45RO-CCR7+CD62L+CD27+CD45RA+) and central memory (TCM: CD45RO+CCR7+CD62L+CD27+CD45RA-) subsets in CD4 cells, and TCM in CD8 cells. Terminally differentiated effector memory (CD45RO-CCR7-CD62L-CD45RA+) cells increased in both lineages. CD8 T cells also showed decreased NKG2D expression. During disease progression from PFMF to OMF, there was a further increase in hypermature NK cells and downregulation of DNAM-1 and NKG2A. JAK2-mutated patients showed decreased expression of KIR2DL1 (total and hypermature NK), reduced CD4 T cells, increased CD8 T cells, and decreased CD8 TCM cells. The MPN-exposed group exhibited reduced frequencies of mature NK cells (CD45hiCD19-CD3-CD122+NK1.1+CD49b+NKp46+), NKG2D expression, and T cell frequencies (CD45hiCD19- NK1.1-CD3+), but increased CD8 T cells, with elevated TIM-3 expression.

Discussion and conclusion: These findings reveal distinct immune signatures associated with MF progression and JAK2V617F. NK cell dysfunction, characterized by impaired maturation and loss of activating receptors, may compromise immune surveillance and promote leukemic transformation. Concurrently, T cell alterations suggest chronic inflammation and immunesenescence, particularly in JAK2-mutated cases. The murine model supports a direct role for JAK2V617F-mutant hematopoiesis in driving immune exhaustion. Collectively, our data highlights the contribution of immune dysfunction to MF pathogenesis and progression, providing insights into how molecular heterogeneity may influence disease.

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IMPACT OF ABCB1 AND ABCG2 POLYMORPHISMS ON TROUGH IMATINIB CONCENTRATION IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction: Chronic myeloid leukemia (CML) is a myeloproliferative disorder effectively managed with tyrosine kinase inhibitors (TKIs) like imatinib. However, drug resistance and suboptimal responses remain challenges. Polymorphisms in drug transporter genes, such as ABCB1 and ABCG2, can influence imatinib plasma concentrations and treatment outcomes. **Objectives:** The primary research question was: "Is there an association between polymorphisms in the ABCB1 and ABCG2 genes and imatinib plasma concentration in patients with chronic myeloid leukemia?" **Material and methods:** We searched in Medline, Embase, and Web of Science databases for studies that evaluated the association between ABCB1 and ABCG2 polymorphisms and imatinib plasma concentrations in CML patients. Treatment effects were quantified using the mean difference (MD) with associated 95% confidence intervals (CIs). **Results:** Six studies were included with 654 heterozygous patients, 416 variants, and 470 wild-type. The follow-up ranged from 24 to 83 months. A significant increase in imatinib trough concentration (Ctrough) was observed in patients with the ABCB1 c.3435C>T TT genotype compared to the CC genotype (MD 207.54, 95% CI 101.46-313.62, $p = 0.051$). Additionally, patients with the ABCB1 c.2677G>T GG genotype exhibited significantly higher Ctrough levels compared to both GT (MD 432.52, 95% CI 241.24-623.79, $p = 0.006$) and TT genotypes (MD 396.96, 95% CI 190.12-603.79, $p < 0.001$). For the ABCB1c.1236C>T polymorphism, patients with the TT genotype had significantly lower Ctrough levels compared to TC genotypes (MD -350.50, 95% CI -559.51, -141.50, $p = 0.059$). No significant association was found between the ABCG2 c.412C>A polymorphism and imatinib Ctrough. **Discussion and conclusion:** Genetic polymorphisms of ABCB1 drug transporter proteins play an important role in the serum concentration of imatinib, since some mutations such as variant c.3435C, wild type c.2677G and variant c.1236C showed significant increase Ctrough level when compared to other variants. Mutations of the ABCG2 transporter did not show statistically significant differences. Further studies could be performed to evaluate the impact of implementation of genetic testing on clinical practice.

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IMPORTÂNCIA DO DIAGNÓSTICO INTEGRADO NA DETECÇÃO DE CRISE BLÁSTICA LINFOIDE AO DIAGNÓSTICO DE LEUCEMIA MIELOIDE CRÔNICA

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Introdução: Demonstrar a importância do diagnóstico integrado no diagnóstico de leucemia mieloide crônica no diagnóstico de crise blástica linfoide. **Descrição do caso:** Paciente do sexo feminino, 37 anos, previamente hígida, com relato de astenia, iniciado há um mês, com piora progressiva. Associado ao quadro apresentou síncope sem causa definida. Evoluiu com dor em arco costal direito, o que fez procurar atendimento de saúde. Negava sintomas constitucionais. Apresentava baço palpável a 4 cm do RCE. Durante a avaliação, foi evidenciada leucocitose (leucócitos totais:181.970/mm^3) 50% neutrófilos, 2% monócitos, 1% eosinófilos, 1% de basófilos, 4% promielócitos, 10% mielócitos, 10% metamielócitos, 1% de blasto e 10% linfócitos. Hb 11,2 g/dL, plaquetas 180.000. O mielograma foi sugestivo de LMC em fase crônica, com 3% de blastos; RT-PCR qualitativo para BCR::ABL1 positivo para o transcrito b2a2 (p210), cariótipo 46 XX, t(9;22)(q34;q11). A biópsia de medula óssea, foi hipercelular (>95%), com presença de megacariócitos hipolobulados e áreas com predomínio da série granulocítica com retardo maturativo (padrão fase crônica em 70% da amostra) e outras com proliferação difusa de células imaturas, em 30% da amostra, sugestiva de linhagem linfoide no HE. Padrão de fibrose reticulínica grau 2. A imunohistoquímica foi positiva para CD20, CD79A, PAX-5, CD3, CD5, CD10, CD34 (em cerca de 10% dos precursores imaturos). A citometria de fluxo mostrou a presença de 1,18% de blastos linfoides (CD34+ / CD19+ / nTdT+ / CD66c parcial (42%) / CD10+ / CD22 parcial (54%) / CD9 +) e 0,12% de blastos mieloides, confirmando o diagnóstico de crise blástica linfoide B. Nas tomografias computadorizadas de tórax e abdome foram visualizados esplenomegalia de 15 cm, lesões líticas em corpos vertebrais, sacro e bacia, evidenciados também no PET-CT. A paciente foi submetida a tratamento com Imatinibe associado ao protocolo GRAAPh, com retorno para fase crônica e resposta hematológica completa, sem atingir resposta molecular maior e posteriormente transplante de células-tronco hematopoéticas (TCTH) alogênico. A paciente evoluiu a óbito por choque séptico durante o TCTH. Discussão: o diagnóstico da LMC fase blástica ocorre em menos de 5% dos casos, com maior prevalência da crise blástica mieloide. A WHO 2022 atualmente classifica como crise blástica linfoide os casos com presença de focos de blastos extramedulares ou a presença de linfoblastos, (sem nenhum valor de corte) no sangue periférico ou na medula óssea. O estudo imunohistoquímico na crise blástica linfoide geralmente mostra positividade dos marcadores TdT e CD34 em precursores linfoide, além de marcadores Pan-B como PAX-5 e CD79a nos casos de crise blástica linfoide. Muitas vezes o diagnóstico diferencial entre crise blástica linfoide e LLA Ph+ é difícil, e exige a combinação entre dados clínicos, imunofenotípicos e moleculares, sendo o transcrito p190 mais comum na LLA Ph+. **Conclusão:** Ressaltamos a importância do