e 3 (p = 0.06). Não houve diferença significativa na sobrevida livre de progressão (91% grau 1 vs. 70% grau 2 e 3). Houve um total de 13 óbitos e 7 perdas de seguimento. **Discussão:** Nas recomendações laboratoriais atuais da European LeukemiaNet, a biópsia de medula óssea (BMO) não foi incluida como um exame mandatório para o diagnóstico da LMC. Ao mesmo tempo, a presença de focos de blastos na BMO é um dos critérios para crise blástica e alguns estudos relatam a presença de fibrose de medula óssea como fator de pior prognóstico. No nosso estudo não houve diferença significativa entre os graus de fibrose e SG e SLP, mas observamos menores taxas de SG e SLP nos casos com fibrose graus 2 e 3. Uma das limitações foi a falta de informação suficiente nos laudos de BMO para realizar a classificação da fibrose ou a não disponibilidade da BMO ao diagnóstico, reduzindo a casuística. **Conclusão:** Não houve diferença significativa de SG e SLP de acordo com os graus de fibrose encontrados ao diagnóstico em BMO de pacientes com LMC.

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CYTOTOXIC IMMUNE CELLS MATURATION IN MYELOFIBROSIS: IMPLICATIONS FOR DISEASE PROGRESSION

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Myelofibrosis (MF), driven by JAK/STAT signaling mutations in hematopoietic stem cells, has the worst survival rates among myeloproliferative neoplasms (MPNs), worsening from prefibrotic MF (PFMF) to overt MF (OMF) that often precedes acute myeloid leukemia. Natural Killer (NK) cells have phenotypical alterations that predominate in MF when compared to other MPNs, suggesting that the immune content may contribute to disease burden. We hypothesized that the cytotoxic immune cell profile, along with fibrosis and mutations, drives MF progression. Aiming test this, peripheral blood mononuclear cells (PBMC) from 9 PFMF and 9 OMF, and 9 healthy donors (controls: CT) were analyzed by flow cytometry to profile: NK cell frequency and subtypes ($CD45^{hi}CD3^{-}CD19^{-}CD56^{bright}CD16^{-}$; $CD45^{hi}CD3^{-}CD19^{-}CD56^{dim}CD16^{+}$; NK maturation [$CD11b^{-}CD27^{-}$ tolerant (DN), $CD27^{+}CD11b^{-}$ immature secretory (IS), $CD27^{+}CD11b^{+}$ mature secretory (MS), $CD11b^{+}CD27^{-}$ cytotoxic]; T lymphocytes ($CD45^{hi}CD3^{+}$) frequency and subtypes (CD4, CD8) and maturation [$CD45RO^{-}CD45RA^{+}CD27^{+}$ Naïve (N), $CD45RO^{+}CD45RA^{+}CD27^{+}$ intermediate (INT), $CD45RO^{+}CD45RA^{+}CD27^{-}$ Central Effector (CE), $CD45RO^{+}CD45RA^{-}CD27^{+}$ Central Memory (CM)]. Immune evasion was assessed by CD62L, and Treg cells ($CD4^{+}CD25^{hi}CD127^{low}FOxp3^{+}$) were also quantified. NK cytotoxic capacity was measured by quantifying dead/K562 target cells and NK degranulation (CD107a) after PBMC co-culture. Top of FormBottom of Form Total NK frequency was similar in MF vs CT or OMF vs PFMF. $CD56^{bright}$ (CT 3.4 ± 2.6%, MF 17.7 ± 17.9%, $p < 0.05$) were increased and $CD56^{dim}$ (CT 82.7 ± 7.6%, MF 53.4 ± 25%, $p < 0.05$) decreased in MF vs CT. MF showed higher DN (CT 4.5 ± 3.5%, MF 13.9 ± 8.7%, $p < 0.05$) and IS (CT 0.2 ± 0.3%, MF 1.2 ± 1.2%, $p < 0.05$), and lower cytotoxic NK cells (CT 92.1 ± 3.8%, MF 77.3 ± 11.2%, $p < 0.05$). When compared to PFMF, OMF presented higher frequency of cytotoxic NK cells (PFMF 72.2 ± 12%, OMF 82.4 ± 7.9%, $p = 0.09$). In agreement, reduced NK cytotoxic capacity was observed despite no degranulation changing in MF (death: CT 81.8 ± 4.2%, MF 30.1 ± 7.76%, $p < 0.05$) and slightly increased cytotoxicity (PFMF 28 ± 6.4%, OMF 31.4 ± 9.9%, $p = 0.7$) and degranulation (PFMF 10.1 ± 8.8%, OMF 32.17 ± 9.9%, $p = 0.1$) accompanied fibrosis. No changes in total T lymphocytes or CD4/CD8 frequencies were seen between CT and MF or PFMF and OMF. However, INT and CE reduced in MF (CT 19.8 ± 9.9%, MF 7.3 ± 12.2%, $p < 0.05$; CT 19.1 ± 16.4%, MF 8.1 ± 13.8%, $p < 0.05$) and CM decreased in OMF (PFMF 18.9 ± 11.9%, OMF 10.6 ± 9.5%, $p < 0.05$). $CD62L^{+}$ CM decreased in MF (CT 21.5 ± 12.8%, MF 6.8 ± 6.8%, $p < 0.05$) and in OMF (PFMF 9.4 ± 8%, OMF 3.9 ± 3.7%, $p = 0.2$). Treg frequency decreased in MF (CT 1.9 ± 1.7%, MF 0.25 ± 0.22%, $p < 0.05$) but increased in OMF (PFMF 0.2 ± 0.13%, OMF 0.3 ± 0.2%, $p = 0.5$). More advanced MF has a higher degree of fibrosis, which leads to an inflammatory profile. This, in turn, may activate NK cells and result in a more mature but cytotoxic-deficient profile probably due to exhaustion. On the other hand, increased Treg cells found in OMF negatively regulate cytotoxic T cells and its memory compartment, specifically leading to immune evasion via a decrease in $CD62L^{+}$ CM (associated with better anti-tumor response). The results shed light on the mechanisms involved in MF progression, suggesting that changes in the maturation profile of cytotoxic cells is associated with disease progression, thus inspiring new therapies that target antitumoral cells from the leukemic environment.

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ANÁLISE DO PERFIL CLÍNICO DE PACIENTES COM LEUCEMIA MIELOIDE CRÔNICA NO AMAZONAS

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