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SURVIVAL OUTCOMES AND PROGNOSTIC DETERMINANTS IN CHRONIC MYELOID LEUKAEMIA: ANALYSIS OF RISK SCORES, MOLECULAR RESPONSE, AND TREATMENT DYNAMICS

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Introduction: Despite substantial progress in chronic myeloid leukaemia (CML) treatment, long-term survival and progression-free survival (PFS) remain influenced by baseline risk scores and early molecular response. Stratification by scores such as EUTOS, ELTS, and *BCR::ABL1* levels may improve prediction of outcomes and guide treatment. **Objectives:** To assess overall survival (OS) and progression-free survival in a CML cohort, stratified by prognostic scores and molecular response, and to identify predictive markers associated with favourable outcomes. **Material and methods:** Kaplan-Meier analysis was performed for OS and PFS, followed by log-rank tests for group comparisons. Stratification included EUTOS (>87), ELTS (>2.21), and *BCR::ABL1* at baseline (>100%) and month 3 (<10%). Survival curves were interpreted alongside clinical variables and response kinetics. **Results:** The overall survival probability remained above 75% at the end of follow-up, with a gradual decline from month 20. Stratified analysis showed significantly worse OS for patients with EUTOS >87 ($p = 0.014$), while ELTS >2.21 showed a non-significant trend toward poorer survival ($p = 0.084$). Baseline *BCR::ABL1* >100% was not associated with OS differences. For PFS, approximately half the cohort remained progression-free at the final follow-up. EUTOS >87 was significantly associated with lower PFS ($p = 0.023$), while ELTS >2.21 again showed a non-significant trend ($p = 0.082$). Baseline *BCR::ABL1* >100% did not predict PFS ($p = 0.693$). In contrast, achieving molecular response <10% at month 3 (MR3) was significantly associated with superior PFS ($p = 0.005$). **Discussion:** The findings highlight the prognostic importance of the EUTOS score for both OS and PFS. While ELTS showed a consistent trend towards worse outcomes, it did not reach statistical significance. The most robust predictor of long-term disease control was early molecular response (MR3 <10%). Baseline *BCR::ABL1* >100% did not predict survival outcomes, potentially due to early therapeutic adjustments in this subgroup. **Conclusion:** In this real-world cohort, high EUTOS scores and failure to achieve MR3 <10% were key markers of poor prognosis. *BCR::ABL1* baseline level was the strongest predictor of early molecular response, while early response itself emerged as a relevant factor for long-term disease control. The integration of molecular and clinical risk parameters remains essential for optimising CML management.

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TERAPIAS COMBINADAS EM MIELOMA MÚLTIPLO E LEUCEMIAS RESISTENTES: AVANÇOS E PERSPECTIVAS EM TRATAMENTOS PERSONALIZADOS

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Introdução: O mieloma múltiplo (MM) e as leucemias resistentes constituem um importante desafio terapêutico na hematologia moderna. Apesar de avanços significativos nas últimas décadas, a evolução natural dessas doenças ainda é marcada por recaídas frequentes e pelo desenvolvimento de resistência aos tratamentos disponíveis. O MM, uma neoplasia maligna das células plasmáticas, apresenta um curso clínico heterogêneo, com sobrevida global variável, mesmo em pacientes submetidos a regimes de alta intensidade. As leucemias resistentes, por sua vez frequentemente demonstram escape às terapias de primeira e segunda linha, motivando a busca por estratégias inovadoras. Nesse contexto, as terapias combinadas, integrando agentes com diferentes mecanismos de ação, têm emergido como alternativa promissora. Além disso, a personalização dos esquemas, baseada em

biomarcadores moleculares e perfis genômicos, vem possibilitando um manejo mais preciso, alinhado aos princípios da medicina de precisão. **Objetivos:** Revisar e discutir os avanços recentes no uso de terapias combinadas no tratamento do mieloma múltiplo e de leucemias resistentes, destacando seu potencial na abordagem personalizada. **Material e métodos:** Este estudo consiste em uma revisão narrativa da literatura. Foram realizadas buscas nas bases PubMed, Scopus e Web of Science entre janeiro de 2018 e julho de 2025, utilizando os descritores: multiple myeloma, drug resistance, leukemia, combination therapy, personalized medicine e precision oncology. Foram incluídos artigos originais, revisões sistemáticas e estudos clínicos relevantes publicados em inglês ou português. Estudos pré-clínicos foram considerados para análise mecanística. **Discussão e conclusão:** A resistência terapêutica no mieloma múltiplo (MM) e nas leucemias resistentes é multifatorial, envolvendo mutações (TP53, KRAS, NRAS, FLT3, IDH1/2), alterações epigenéticas e suporte do microambiente tumoral, que favorecem a sobrevivência e reduzem a eficácia dos tratamentos. A ativação de vias como NF-κB e a ação de citocinas (IL-6, TNF-α) aumentam a refratariedade. As terapias combinadas no MM evoluíram de dupletos para tripletos e quadrupletos (ex.: DRd, KRd, DVRd), integrando imunomoduladores, inibidores de proteassoma, corticosteroides e imunoterapias avançadas como CAR-T anti-BCMA e anticorpos biespecíficos. No tratamento de leucemias resistentes, destacam-se associações de inibidores de FLT3 com agentes hipometilantes (LMA) e imunoterapias combinadas anti-CD19 e anti-CD22 (LLA), além de CAR-T com inibidores de checkpoint. No futuro, IA e big data devem otimizar a escolha de combinações, apoiados por ensaios clínicos adaptativos. As pesquisas buscam integrar agentes epigenéticos, imunomoduladores de nova geração e drogas que modulam o microambiente, com atenção à mitigação de toxicidades e validação em estudos multicêntricos internacionais. As terapias combinadas representam uma das mais promissoras fronteiras no tratamento do mieloma múltiplo e das leucemias resistentes. Ao integrar agentes com mecanismos de ação distintos, é possível abordar simultaneamente múltiplas vias de resistência, aumentar as taxas de resposta e prolongar a sobrevida dos pacientes. Essa abordagem, embora mais complexa, se mostra superior à utilização de monoterapias em contextos de alta refratariedade.

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THE GAB2 NETWORK IN ACTION: UNVEILING GAB2, GRB2, PIK3R1, AND LYN IN CHRONIC MYELOID LEUKEMIA

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Introduction: Chronic Myeloid Leukemia (CML) is a myeloproliferative disorder driven by the BCR::ABL1 fusion kinase, resulting from a t(9;22) translocation. Tyrosine kinase inhibitors (TKIs) revolutionized CML therapy, yet some patients develop resistance or show a suboptimal response. While ABL1 mutations underlie BCR::ABL1-dependent resistance, independent mechanisms remain unclear. GAB2, a key adaptor protein downstream of growth factor receptors and BCR::ABL1, activates MAPK and PI3K pathways, contributing to CML pathogenesis and TKI resistance. **Objectives:** To evaluate the role of GAB2 as potential biomerkers in CML and its interacting network. **Material and methods:** Potential functional partners of GAB2 were evaluated using the STRING database and transcriptomic datasets from GEO database (GEO ID: GSE33075). GAB2 itself and its interacting partners (GRB2, PIK3R1 and LYN) were analysed using qPCR in peripheral blood samples from CML patients in distinct stages of the disease: Diagnosis, Treatment-free remission (TFR), Imatinib - Good therapy response (Imatinib-GTR), Imatinib - Bad therapy response (Imatinib-BTR), patients with T315I mutation (T315I), and health controls (HC). Statistical models (Kruskall-Wallis, Dunn's post-test, Pearson Correlation and Simple Linear regression) were performed to evaluate the potential of the network. **Results:** String interaction database revealed eleven proteins were associated to GAB2, which were evaluated in the GEO dataset, from which GAB2, GRB2, PIK3R1 and LYN were selected for qPCR analysis in peripheral blood of CML patients. Interestingly, this analysis revealed that all those genes were highly expressed in samples of healthy controls (GAB2: $P < 0.0001$, GRB2: $P < 0.0001$ and LYN: $P = 0.02$) and in good responder groups, which included TFR and IM-GTR (for TFR: GAB2: $P < 0.0001$, GRB2: $P < 0.0001$, PIK3R1: $P < 0.0001$ and LYN: $P < 0.0001$ and for IM-GTR: GAB2: $P < 0.0001$, GRB2: $P = 0.004$, PIK3R1: $P = 0.005$ and LYN: $p = 0.03$), while showing lower expression in IM-BTR) (Figure A, clinical samples evaluation). Our results showed a linear regression in the decreasing expression pattern of GAB2 and partners for good therapy responders, diagnosis and bad therapy responders (R2 for GAB2: 0.9, GRB2: 0.9, PIK3R1: 0.8 and LYN: 0.7), demonstrating strongly the relation between the four genes and CML and the possible network of GAB2, GRB2, LYN and PIK3R1 (Figure B, linear regression). Additionally, samples from patients harbouring a BCR::ABL1 T315I mutation showed an up- regulation of the 4-gene panel when compared to IM-BTR, which did not harbour the T315I mutation (GAB2: $p < 0.0001$, GRB2: $p < 0.0001$, PIK3R1: $p = 0.0003$ and LYN: $p = 0.02$), showing a possible activity of GAB2 and partners as a BCR::ABL1-independent mechanism of resistance. **Discussion and conclusion:** Our study reveals a strikingly coordinated expression pattern among GAB2 and its key interaction partners—GRB2, PIK3R1, and LYN—in clinical samples from CML patients. Notably, these patterns were not only consistent but also significantly