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MODIFICATIONS IN RISK CLASSIFICATION OF ACUTE MYELOID LEUKEMIAS UNDERGOING LESS INTENSIVE CHEMOTHERAPY COMPARING THE 2022 AND 2024 STRATIFICATIONS OF THE EUROPEAN LEUKEMIANET AND THEIR IMPACT ON TREATMENT DECISION, RESPONSE RATES AND OUTCOMES OF A BRAZILI

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Introduction: Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy with a genetic variability that plays a role in determining clinical outcomes. The 2022 European LeukemiaNet (ELN) model uses molecular data to stratify risk in patients receiving high-intensive induction with or without allogeneic hematopoietic stem cell transplantation (allo-SCT), however, its predictive value is limited in those treated with less-intensive induction (Venetoclax plus hypometilating agents-HMA). Due to this gap, a 2024 model based mostly on VIALE-A study stratified patients into three groups: (1) TP53 mutations are classified as adverse risk;(2) mutations in FLT3-ITD, NRAS, or KRAS, or other mutations not classified as favorable or adverse, are intermediate risk; and(3) the presence of NPM1, IDH1, IDH2 or DDX41– or the absence of intermediate or adverse risk changes are considered favorable-risk. Yet, this remains suboptimal considering that mutations classified as adverse in ELN2022 may not carry the same poor prognostic impact in patients treated with less-intensive induction. Also, HMA plus Venetoclax is now used in a more heterogeneous population than in VIALE-A. **Objetivos:** Evaluate risk reclassification by mutation profiles and the impact in treatment response and outcomes in AML patients receiving less-intensive induction in a brazilian Center. **Material and methods:** A retrospective analysis was made with electronic medical records of patients diagnosed with AML in our center that received induction with Venetoclax and Azacytidine and had molecular biology evaluated by next-generation sequencing (NGS) or Fluorescence In Situ Hybridization. **Results:** We included 29 patients with AML diagnosed between 2018-2024. The median age was 70 years, with a male predominance (62%). 16 patients (55%) were classified as eligible for allo-SCT. 7 patients (24%) were therapy-related AML and 12(41%) were considered as a secondary progression from Myelodysplastic Syndrome. The most frequent mutations identified were TP53(26%) and ASXL1(24%), mutations in IDH2, SRSF2, and STAG2 were each detected in 21% of cases. According to the ELN2022, 25 patients (86%) were classified as adverse-risk, 3 (10%) as intermediate-risk, and only 1 (3%) as favorable-risk. However, based on the ELN2024, 17 patients (59%) were reclassified as intermediate-risk, 8 (26%) as adverse-risk, and 4 (14%) as favorable-risk. 1 case initially categorized as intermediate-risk by ELN2022 was reclassified as favorable-risk by the ELN2024, and 15 patients originally assigned to the adverse-risk group were reclassified as intermediate-risk. Risk classification remained unchanged in only 11 cases (38%). 23 patients (79%) achieved a hematologic response, of which 14 presented negative measurable residual disease, the majority (64%) after the first cycle. Only 3 patients (10%) were refractory to treatment, one of them still alive at last follow-up.15 patients underwent allo-SCT as consolidation therapy.At their last follow-up,6 patients relapsed, 3 during treatment and 3 post allo-SCT, 9 maintained response, 15 patients (52%) died and 4 cases were lost at follow-up. The median time from diagnosis to relapse was 8.3 months, and 2.7 months between relapse and death, with a follow up of 11.1 months from diagnosis to death. **Discussion and conclusion:** In a developing country hospital without routine NGS access, accurate molecular classification is limited, and reaching a large sample of patients can be challenging, demonstrating the importance of adequate risk stratification for these patients.

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MOLECULAR ANALYSIS OF THE TP53 R248Q MUTATION: IMPACT ON P53–APR-246 INTERACTION IN AML

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Introduction: A previous study identified 65 TP53 variants in AML patients from TCGA and BeatAML cohorts, with R248Q being the most frequent. This mutation is a known hotspot, functionally dominant-negative, and predicted to be pathogenic. Although structural analyses show no major changes, evidence indicates it impairs p53 function. Synergism assays identified Kasumi1 as the optimal model. **Objetivos:** This study aimed to assess whether APR-246 reactivates mutated p53 in Kasumi1 (R248Q) cells and to evaluate its effects combined with clinically relevant chemotherapeutics. **Material and methods:** Kasumi1 cells were cultured in RPMI with 20% FBS and treated with APR-246 (0, 2.5, 5, 10 μM) for 72 hours. For combination assays, cells received: (i) 0 or 6.25 μM APR-246; (ii) 0.5 μM cytarabine alone or with APR-246; (iii) 0.06 μM daunorubicin alone or combined; (iv) 1.25 μM venetoclax alone or combined with APR-246. After treatment, cells were centrifuged, washed with PBS, and pellets used for protein extraction with lysis buffer (Tris-HCl, Triton X-100, PMSF, Na_3VO_4, NaF, $Na_4P_2O_7$, EDTA). Samples were incubated on ice, centrifuged, run on SDS-PAGE, transferred to nitrocellulose, blocked with 5% skim milk, incubated with primary and HRP-conjugated secondary antibodies, and detected by ECL™ according to manufacturer instructions. **Results:** Upon increasing concentrations of APR-246, we assessed the expression of key proteins, including p53 (drug target), BAX

(pro-apoptotic marker), p21 (a p53- responsive cell cycle regulator), γH2AX (marker of DNA damage), PARP1 (apoptosis marker), SQSTM1/p62 and LC3B (autophagy markers), and α-tubulin (loading control). APR-246 treatment resulted in a dose-dependent reduction in p53, p62, and LC3B-I/II levels, accompanied by upregulation of BAX, p21, and cleaved PARP1, indicating induction of apoptosis and autophagic flux. Notably, combination treatments further increased γH2AX levels and PARP1 cleavage compared to single-agent controls, suggesting a synergistic enhancement of DNA damage and apoptotic signaling. **Discussion and conclusion:** These findings corroborate literature reports that APR-246 restores mutated p53 functionality. The observed p53 decrease may result from reactivation, leading to negative feedback-mediated degradation pathways. Enhanced apoptotic and cell cycle arrest markers, coupled with reduced autophagy proteins, confirm pathway restoration. Synergistic effects in combination assays emphasize APR-246's potential as an adjuvant to standard chemotherapy in TP53-mutated AML. APR-246 exhibits functional activity in Kasumi1 cells harboring the TP53 R248Q mutation by promoting apoptosis, reducing autophagy, and increasing DNA damage. Its combination with drugs in clinical settings potentiates these effects, underscoring synergistic therapeutic potential. Future studies will include in silico docking, molecular dynamics simulations, and in vitro complementary molecular analyses such as apoptosis assays and PCR-based gene expression.

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MORTALIDADE POR LEUCEMIA LINFOIDE EM IDOSOS NA REGIÃO SUDESTE DO BRASIL (2020-2024)

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Introdução: A leucemia linfoide é uma neoplasia maligna que apresenta uma proliferação de linfoblastos na medula óssea, que derivam de células linfoides B ou T imaturas. Com o envelhecimento da população, o diagnóstico de doenças onco-hematológicas tem aumentado e representam maior mortalidade e menor sobrevida nessa população comparado com pacientes jovens. **Objetivos:** O estudo tem como objetivo analisar a mortalidade por leucemia linfoide em idosos na região sudeste comparando os dados com a estimativa nacional no período de 2020 a 2024. **Material e métodos:** Estudo descritivo retrospectivo com dados do Painel de Monitoramento de Mortalidade do Departamento de Análise Epidemiológica e Vigilância de Doenças Não Transmissíveis (DAENT/SVSA/MS) durante os anos de 2020 a 2024. Foram coletados dados de mortalidade por leucemia linfoide (C91) em idosos com idades: 60-69, 70-79 e maiores de 80 anos. Foram filtrados os sexos masculino, feminino e "todos" para verificação. **Resultados:** No grupo com idade entre 60-69 anos, foram computados no Brasil 1434 óbitos. O Sudeste corresponde a 48,6% dos casos, sendo SP o estado com maior número de óbitos (26%) seguido de MG (12%). Nessa região, a maioria dos óbitos são em homens, sendo 29% do total representado no Brasil. O estado de SP tem maioria dos acometidos sendo do sexo masculino. Na faixa etária de 70 - 79 anos, o país registrou 1741 óbitos, sendo 45% no Sudeste. O estado de SP lidera, representando 23%, seguido de MG com 12%. O estado com menor número foi o ES (1,8%). O sexo masculino é o mais afetado nesse grupo na região (26%), sobretudo em SP. No público maior de 80 anos, tem-se mortalidade no Brasil de 1751 pessoas. O Sudeste obteve maior porcentagem (46%), com predomínio em SP (24%) e MG (11%). O estado do ES registrou menor mortalidade (1,4%). Ao contrário do observado anteriormente, as mulheres foram as principais vítimas nesse grupo, sendo registrados no brasil 882 casos em cinco anos analisados. O Sudeste também obteve o maior número como sendo mulheres, sendo 24% do total registrado no Brasil para essa idade. **Discussão e conclusão:** Percebe-se um comportamento similar no sexo atingido por mortalidade nas faixas etárias de 60-69 e 70-79 anos, sendo o público masculino como principal acometido, variando apenas em maiores de 80 anos. Na lógica de estados, SP e MG lideram em número de óbitos em todas as faixas etárias, e o ES com menor mortalidade registrada em todos os cenários. O Sudeste obtém o número superior a 45% de mortalidade por leucemia em idosos, sendo a região com maior quantidade de óbitos no Brasil, nessa faixa etária. Com relação a mortalidade por leucemia na população geral na região Sudeste, o dado citado é superior a 40%. A mortalidade por leucemia linfoide é causa de grande mortalidade em idosos na região Sudeste, aumentando o risco com o avançar da idade. É necessário o desenvolvimento de pesquisas que analisem o perfil epidemiológico desses pacientes para melhores desfechos e fomento de políticas públicas em saúde, haja vista o aumento do envelhecimento na população brasileira.

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