ASSESSMENT OF THE FEASIBILITY AND SAFETY OF ASSISTED CALORIC RESTRICTION (FMD) IN PATIENTS WITH MYELODYSPLASTIC NEOPLASMS

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Diet, sedentary lifestyle, and overall lifestyle are among the primary risk factors for the onset of cancer and have been a challenge for scientific research for decades. Adverse events in oncological treatments are related to their nonspecificity to tumor cells and the cytotoxic effects on normal cells. Therefore, searching for therapies that promote greater efficacy and reduce treatment side effects is continuous. In this search, the *Fasting Mimicking Diet* (FMD) protocol has gained prominence as it presents a low-calorie, low-protein, and moderate to high unsaturated fat composition. This study evaluated the applicability, feasibility, and safety profile of the nutritional intervention, FMD diet combined with Azacitidine in treating patients with Myelodysplastic neoplasms (MDS). We conducted non-randomized experimental clinical research. The dietary intervention was assessed using anthropometric data, toxicity, and laboratory tests in patients diagnosed with MDS. Twenty-one patients were selected at the first cycle, with an average age of 68 (± 14) years. The FMD diet was used for 12 patients. Nine cases were excluded due to death or inability to maintain the diet protocol. The average weight of the patients was 61.24 kg, and the average BMI was 23.83. In the second treatment cycle, the average weight and BMI were 58.91 kg and 22.71, respectively. Both the 2.33 kg weight loss and the reduction in average BMI were significant ($p = 0.020$ and $p = 0.040$, respectively). In the third cycle, the average weight was 57.28 kg, and the BMI was 22.57, with another significant weight reduction ($p = 0.013$). During the application of the FMD, hematological markers (hemoglobin, mean red blood cell volume, leukocytes, segmented neutrophils, and platelets) were evaluated before and after chemotherapy, showing no change in the hematological profile of patients after chemotherapy with the FMD diet ($p > 0.05$ for all values). This result demonstrated that weight loss and BMI reduction were not clinically impactful in the patients in our cohort. Finally, among the patients who followed the FMD diet, there was a significant reduction in the severity of constipation cases ($p = 0.014$). These results suggest that the FMD Diet is feasible for patients with Myelodysplastic neoplasms and should be evaluated in Phase 2 and Phase 3 studies.

https://doi.org/10.1016/j.htct.2024.09.753

MIELOFIBROSE IDIOPÁTICA NA CRIANÇA: UM RELATO DE CASO

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Introdução: A mielofibrose (MF) é uma doença mieloproliferativa BCR-ABL negativa, caracterizada por leucoeritroblastose, fibrose medular, anemia e fraqueza. Pode evoluir para sudorese noturna, astenia progressiva, perda de peso, icterícia e dores ósseas. É uma patologia rara, mais prevalente em idosos, sendo incomum na infância, com menos de 100 casos descritos nesta população até o momento. Pode ser classificada como primária ou secundária, quando desencadeada por policitemia vera, trombocitemia essencial ou infecções. Em pediatria, a MF se apresenta de maneira distinta da observada em adultos e é considerada um diagnóstico de exclusão. Apesar de existirem critérios diagnósticos para adultos, não há consenso sobre critérios específicos para pacientes pediátricos. **Objetivos:** Apresentar aspectos clínicos, anatomopatológicos e moleculares de um paciente pediátrico com suspeita de MF primária que podem auxiliar na definição de futuros critérios definidores para a doença. **Métodos:** Foram analisados dados clínicos e laboratoriais de um paciente pediátrico com suspeita de MF, de setembro de 2023 a abril de 2024. **Resultados:** Paciente, sexo masculino, 12 anos, apresentou febre, pancitopenia, hepatoesplenomegalia, amigdalite, linfonodomegalia cervical, lesões de pele eritematosas, necróticas e ulceradas, artrite em ombro direito, consolidação em ápice de pulmão esquerdo e perda de peso de 13kg. A investigação laboratorial afastou doenças autoimunes e infecções por microrganismos que culminam em falência medular. As biópsias de pele, linfonodo e osso, realizadas em outubro de 2023, mostraram achados inespecíficos. A biópsia de medula óssea (BMO) com imunohistoquímica evidenciou neoplasia mieloproliferativa, com série megacariocítica hipercelular, formação de agregados frouxos, fibrose reticulínica (MF-2) e ausência de blastos. Os exames BCR-ABL e JAK2 foram negativos. O exoma revelou variantes de significado incerto dos genes BRCA2 e RAD50. Uma nova BMO em dezembro de 2023 identificou apenas discreta hipocelularidade e o painel NGS para doenças mieloproliferativas (incluindo os genes ASXL1, BCOR, CALR, CEBPA, ETVG, EZH2, IKZF1, NF1, PHF6, PRPF8, RB1, RUNX1, SH2B3, STAG2, TET2, TP53, ZRSR2, ABL1, BRAF, CBL, CSF3R, DNMT3A, FLT3, GATA2, HRAS, 1DH1, IDH2, JAK2, KIT, KRAS, MPL, MYD88, NPM1, NRAS, PTPN11, SETBP1, SF3B1, SRSF2, U2AF1 e WT1) não detectou mutações. Foi realizado tratamento suportivo e antibioticoterapia, com melhora clínica e laboratorial progressivas, levando à principal suspeita de MF primária com resolução espontânea. **Discussão:** A falta de critérios diagnósticos bem estabelecidos

para a população pediátrica e a manifestação distinta da doença nesse grupo tornam o diagnóstico desafiador. Mishra (2020) relata uma série de casos em que a maioria dos pacientes pediátricos com MF apresentou-se com anemia, hepatoesplenomegalia, ausência de causas secundárias para a doença, ausência de leucoeritroblastose e com resultado negativo para JAK2. Esses achados são semelhantes aos observados no presente relato e fortalecem o diagnóstico de MF primária, assim como ajudam a ressaltar as diferenças em relação à apresentação típica da doença em adultos. **Conclusão:** Dada a raridade, complexidade e diferenças na apresentação quando comparada a pacientes adultos, é de suma importância o consenso em relação aos critérios diagnósticos da MF em pediatria, objetivando o aprimoramento da condução desse quadro.

https://doi.org/10.1016/j.htct.2024.09.754

THE ATAXIA-TELANGIECTASIA MUTATED (ATM) GENE PLAYS A PIVOTAL ROLE IN THE REPAIR OF DNA IN CASES OF MYELODYSPLASTIC NEOPLASM

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Myelodysplastic Neoplasm (MDS) is an age-associated neoplasia characterized by frequent epigenetic abnormalities being hypermethylation the most common, frequently associated with transformation to acute myeloid leukemia (AML). DNA repair genes have been constantly downregulated in MDS during progression to AML, but these genes have not been evaluated regarding methylation status or mutational profile. Using three different cohorts of MDS (Cohort A- 56 patients; Cohort B- 100 patients; Cohort C- 76 patients) in three sequential steps we evaluated with complementary methods (pyrosequencing, real-time PCR, immunohistochemistry, cytogenetics and search of mutations) the DNA repair genes for the following analyses: methylation of single-strand (*XPA, XPC, XPG-ERCC5, CSA-ERCC8*, and *CSB-ERCC6*) and double-strand (*ATM, BRCA1, BRCA2, LIG4*, and *RAD51*) DNA repair genes by pyrosequencing; gene expression by RT-qPCR of the *ATM* gene; and protein expression by immunohistochemistry of ATM, 5-methylcytosine (5mC), and 5-hydroxymethylcytosine (5-hmC). Additionally, we used cBioPortal to search for mutations in single-strand and double-strand DNA repair genes. Regarding methylation of single strand repair genes, we detected *XPA* with higher methylation for low risk MDS than high risk MDS ($p < 0.0001$) while for double-strand repair pathway, only *ATM* showed higher methylation for patients who transformed to AML compared to cases who did not transform into AML ($p = 0.016$). In a second step, we evaluated the gene expression of ATM, showing downregulation in MDS compared to controls ($p = 0.042$). In a third step, when we divided patients according to WHO classification of 2022, we detected a progressive reduction of *ATM* expression from subtypes considered as low risk disease (Hypoplastic MDS, MDS with Ring Sideroblasts, MDS with deletion (5q)) compared to high risk MDS (increased of blasts 1 and 2) and AML. We also detected patients who transformed into AML showed a higher ratio of 5mc/5hmC than cases who did not transform ($p = 0.045$). In addition, we observed a higher tissue methylation score (M-score of 5mC%) in patients classified as poor cytogenetic risk by the IPSS-R than patients classified as good cytogenetic risk ($p = 0.035$). Finally, using the most recent platform CBioportal (including the cases of Molecular IPSS with more than 7000 patients), we detected *ATM* as the most mutated, among the DNA repair genes, with the greater variety of mutations such as frameshift, missense and splice compared to others and only *ATM* mutations were classified as oncogenic according to the standards for the classification of pathogenicity of somatic variations in cancer (SOP 2022). We believe all the results presented herein suggest that *ATM* is silenced or down regulated in MDS by methylation or mutations, ultimately increasing the chance of AML transformation.

https://doi.org/10.1016/j.htct.2024.09.755

SJÖGREN-LARSSON SYNDROME ASSOCIATED WITH MYELODYSPLASTIC SYNDROME: A CASE REPORT

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Introduction: The Sjögren-Larsson Syndrome (SSL) is a rare autoimmune disease that causes glandular inflammation, normally in salivary and lacrimal glands. It can be classified as primary, when it is isolated, or secondary, when it is concomitant with other syndromes. Several studies correlate immune diseases with bone-marrow neoplasias, between them, the Myelodysplastic neoplasms (MDS). MDS is a heterogeneous group of hematologic diseases characterized by cytopenias in one or more hematologic lineages. Also, immunological disorders and chronic immunological stimulation are shown to be a trigger to ineffective hematopoiesis in patients with genetic predisposition. This report aims to describe MDS diagnosis in a patient with a rare immune disease and to demonstrate the complications associated with this condition. Case report: A 76-year-old woman, diagnosed with secondary SSL and autoimmune hemolytic anemia