imunofenotipagem de sangue periférico e de medula óssea confirmaram o diagnóstico de LGL-T. Caso 2: Jan/2013: Paciente PM, 53 anos, masculino, francês, branco é avaliado por apresentar alteração laboratorial (neutropenia) detectada em hemograma realizado em 2011. Refere que fez exame de medula óssea na ocasião por indicação de hematologista externo, com resultado final de mielodisplasia. Nega sintomas específicos, alega que possui como história pregressa hipertensão com controle adequado e diverticulose colônica. Hemograma realizado no hospital demonstrou anemia leve (11 Hb/ 32 Hct), leucopenia (3300), neutropenia (660 absoluto / 20% relativo) e contagem relativa de leucócitos alterada (69%). Possuía ao exame físico esplenomegalia com baço palpável à 2 cm do RCE. Hematoscopia de sangue periférico demonstrou presença predominante de LGL's. Exame imunofenotípico de sangue periférico, pesquisa do rearranjo do receptor de células T e medula óssea confirmaram o diagnóstico. Caso 3: Maio/2023: Paciente ESN, 61 anos, masculino, brasileiro, branco é avaliado por apresentar anemia e esplenomegalia. Sem queixas específicas. Novo hemograma mostrou anemia (Hb 10.6 / Hct 32) e leucopenia (2450) com 53% de segmentados e 37% de linfócitos, contagem de plaquetas normal. Hematoscopia de sangue periférico mostrou presença de linfócitos com vilosidade e granulações citoplasmáticas. Imunofenotipagem de SP confirmou o diagnóstico de leucemia de grandes células granulares T. **Discussão e conclusão:** A leucemia de grandes células granulares é uma doença rara e heterogênea, cujo diagnóstico desafia mesmo os mais experientes hematologistas. Por se tratar de uma doença rara e sem um padrão de apresentação clínica muito específico, o diagnóstico se torna difícil e muitas vezes não é levado em consideração. A suspeita clínica do diagnóstico de leucemia de grandes células granulares não deve se concentrar apenas na quantidade absoluta de linfócitos, uma vez que não há um número absoluto ou relativo que seja determinante para o diagnóstico, como é o caso da leucemia linfoide crônica. Nesse sentido, alterações laboratoriais como neutropenia, anemia, trombocitopenia e/ou achados clínicos de hepatoesplenomegalia ou mais raramente linfonodomegalia podem ser pontos cardinais para a elaboração de um pensamento etiológico em que a realização da hematoscopia de sangue periférico pode estreitar as possibilidades e levar ao diagnóstico final.

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EFFICACY AND SAFETY OF NEMTABRUTINIB VERSUS CHEMOIMMUNOTHERAPY IN PATIENTS WITH PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA WITHOUT TUMOR PROTEIN 53 ABERRATIONS: THE OPEN-LABEL, RANDOMIZED, PHASE 3 BELLWAVE-008 STUDY

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Objectives: Standard of care for patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) include fludarabine plus cyclophosphamide and rituximab (FCR) or bendamustine plus rituximab (BR). Targeting Bruton's tyrosine kinase (BTK) has revolutionized the first-line treatment options for CLL/SLL. Nemtabrutinib is a noncovalent, reversible, competitive inhibitor of BTK that targets both wild-type and C481S-mutant BTK. Manageable safety and preliminary antitumor activity of nemtabrutinib has been demonstrated in patients with CLL/SLL in an ongoing, open-label, phase 1/2 dose-escalation study (BELLWAVE-001). BELLWAVE-008 is an open-label, randomized, phase 3 study (NCT05624554) designed to evaluate efficacy and safety of nemtabrutinib compared with investigator's choice of chemoimmunotherapy (FCR or BR) in patients with treatment-naive CLL/SLL without TP53 *aberrations*. **Materials and methods:** Eligible patients are ≥18 years old with treatment-naive, active CLL/SLL and without TP53 aberrations (17p deletion and/or *TP53* mutation) and an ECOG PS of 0-2. Patients with Richter transformation, active central nervous system involvement, or a history of severe bleeding disorder are excluded. Approximately 300 patients will be enrolled and randomly assigned 1:1 to receive nemtabrutinib (65 mg orally once daily until progressive disease, unacceptable toxicity, or discontinuation) or intravenous infusion of the investigator's choice of chemoimmunotherapy for 6 cycles lasting 28 days each (fludarabine 25 mg/m^2 and cyclophosphamide 250 mg/m^2 on days 1, 2, and 3 of each cycle, plus rituximab 375 mg/m^2 initially, followed by 500 mg/m^2 on day 1 of each cycle; or bendamustine 70-90 mg/m^2 on days 1 and 2 of each cycle plus rituximab 375 mg/m^2 initially, followed by 500 mg/m^2 on day 1 of each cycle). Randomization will be stratified by risk (high risk [11q deletion and/or immunoglobulin heavy-chain variable region unmutated] vs low risk [absence of high-risk factors]) and age (<65 years vs ≥65 years). Tumor response assessment via imaging, physical examination, constitutional symptoms, hematologic evaluation, and bone marrow biopsy, as required, will be performed every 12 weeks up to and including cycle 25, and every 24 weeks thereafter or more frequently if clinically indicated. Adverse events will be monitored up to 30 days after treatment cessation (90 days for serious adverse events) and will be graded per NCI CTCAE, version 5.0, and hematologic toxicities will be evaluated according to iwCLL 2018 criteria. The primary end point is progression-free survival per the iwCLL 2018 criteria as assessed by BICR. Secondary end points include overall survival, objective response rate, duration of response, and safety. Exploratory efficacy end points include objective response rate, with partial response with lymphocytosis as a response category, PFS after first subsequent therapy, pharmacokinetics, and health-related quality of life.

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