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Chimeric Diseases' Poorhouse

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An 83-year-old man with an Eastern Cooperative Oncology Group (ECOG) performance score of0 was examined in our unit for leukoneutropenia and thrombocytopenia. The patient's history included pT3N0 rectal adenocarcinoma that was treated surgically one year earlier and was considered to be in remission according to the latest test. The first blood test results revealeda white blood cell (WBC) count of 3.2 G/L, absolute neutrophil count (ANC) of 2.5 G/L, absolute lymphocyte count (ALC) of 0.5 G/L, haemoglobin (Hb) level of 120 g/L with a GMV of 99 fL, reticulocyte count of 21 G/L and platelet (PLT) count of 126 G/L. The patient's renal and hepatic function was normal. LDH levels were also normal. Dixon's test revealed the presence of autoantibodies bound to the platelets. The search for antinuclear antibodies (ANAs) and all viral serology results were negative. Protein electrophoresis revealed an IgM kappa monoclonal peak at 9.6 g/L. The concentration of circulating free kappa light chains was 24 mg/L. The myelogram revealed MDS-EB1 myelodysplasia with 7% blasts, without abnormal lymphoid infiltration, and 3% plasma cells. The medullary lymphoid phenotype showed a polyclonal population. The karyotype was normal, and a molecular biology test (NGS) revealed that the*DDX41* (54%) and *MYD88* (2%) genes were mutated butthat*EVI1/FLT3*-ITD and *NPM1*mutations were absent. We concluded the simultaneous existence of two neoplastic entities: an MDS, intermediate-risk-IPSS, *DDX41* muted (1); and an early-phase non-CLL-type MBL lymphoid (2). Neither of these factors justified a specific treatment; instead, only monitoring was required.

One year later, a new blood test revealed the following parameters: Hb, 120 g/L; WBC count, 2.8 G/L;ANC, 0.8; and PLT count, 113 G/L. The peripheral blast count was 2%. The myelogram revealed a significant increase in blast at 16%, which was classified as MDS-EB2/and high-risk-IPSS (3), and a lympho-plasma cell infiltration estimated at 29%, which was compatible with Waldenström's disease (Fig. 1). The medullary phenotype included CD22+, CD20+, and CD25+ Bcl2- monotypic kappa B-cell populations with a Matutes score of 2/5, which was well matched with Waldenström's disease(4). The karyotype was always normal. Considering the patient's age, recent cancer history, and hostile attitude of the patient toward all forms of chemotherapy, we proposed treatment with venetoclax monotherapy. After the titration phase, the patient received only 200 mg daily. The treatment resulted in complete remission:haemoglobin, 14 G/L; WBC count, 3.6 G/L; ANC, 2.4 G/L; ALC, 0.6 G/L; and PLT count, 140 G/L. The myelogram was normal (Fig. 2). However, the medullary phenotype showedthe persistence of a clonal B population, with only 2% monotypic kappa Blymphocytes. The patient was negative for the MYD88 mutation in the blood but was still positive in the bone marrow. The monoclonal IgM kappa peak decreased to 4.3 g/L. We reduced the dose of venetoclax to 100 mg per day. Eighteen months later, the blood test results were as follows: Hb, 12,9 G/L; VGM, 99 fL; WBC count, 2.66 G/L; ANC 1,8 G/L;ALC 0.63 G/L; PLT count 116 G/L; and a stable monoclonal IgM peak at 4.3 g/L. We considered that the patient was in partial remission according to theInternational Working Group (IWG) criteria. Venetoclax was discontinued. During the treatment, tolerance was correct without significant side effects. Twelve months after discontinuing the treatment, we observed the reappearance of leuko-neutropenia (1.8 G/l), thrombocytopenia (75 G/l), macrocytic anaemia (116 g/l/102 GMV) and 1% circulating blasts. The myelogram revealed 11% blasts. However, the lymphoid phenotype was polyclonal, and the MYD88 L265P mutation was still undetectable; on the other hand, the karyotype revealed trisomy 12. The IgM monoclonal peak remained stable at 4.3 g. Myelodysplastic syndrome relapse was evident, whereas Waldenström's disease showed persistent cytological and molecular remission. Venetoclax treatment was restarted at the same dose of 100 mg per day, allowing new partial remission.

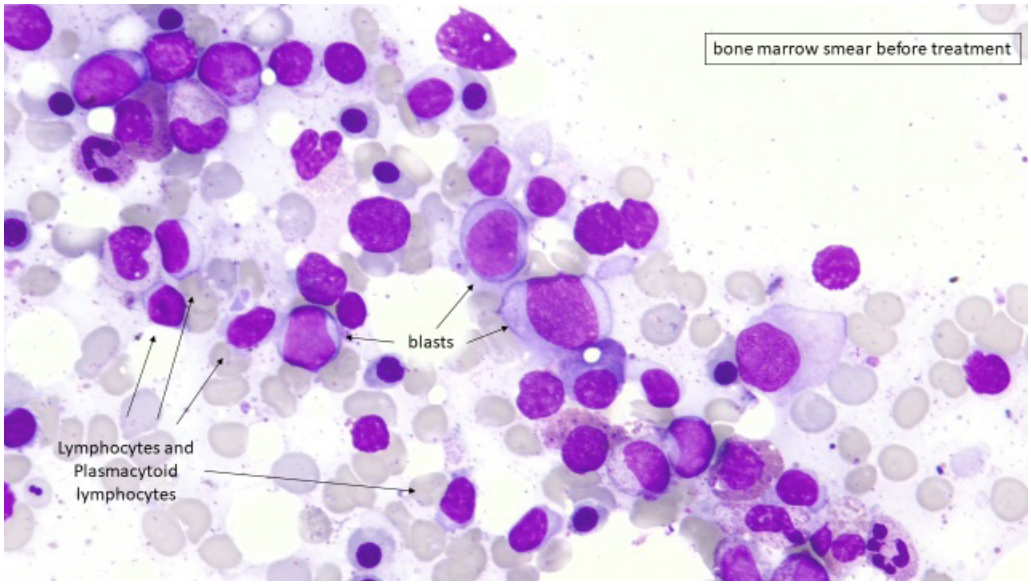

Fig 1. Bonne marrow x1000, before treatment

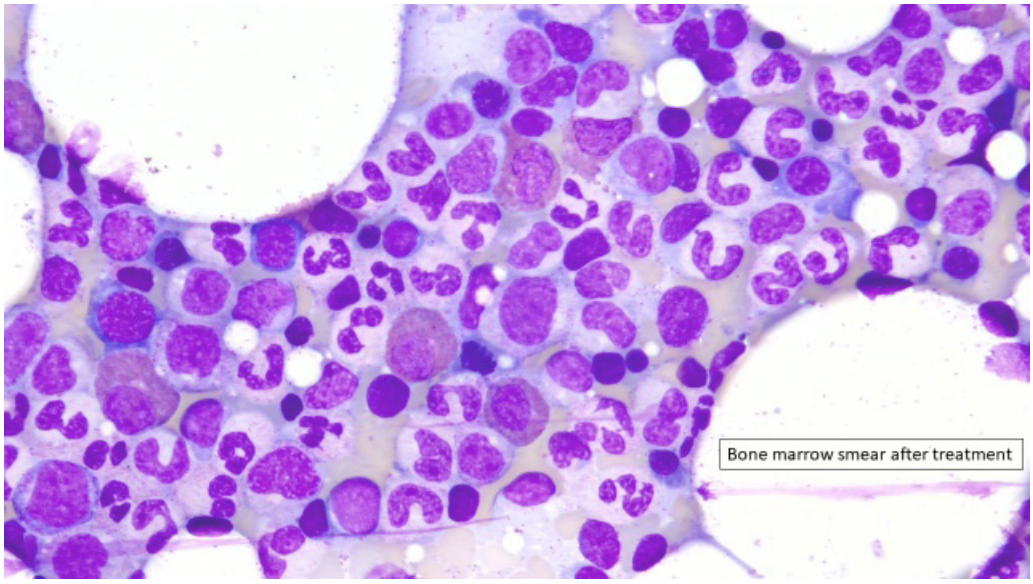

Fig 2. Bonne marrow x1000, after treatment

The efficacy of venetoclax, which is an oral small-molecule B-cell leukaemia/lymphoma-2 (BCL2) inhibitor, in combination with azacitidine has been described in several publications with respect to the treatment of AML in elderly patients who are not eligible for intensive chemotherapy(5). However, the toxicity of this combination has been shown in the phase 3 VIALE-A Clinical Trial: thrombocytopenia occurred in 45% of cases, neutropenia occurred in 42%of cases, febrile neutropenia occurred in 42%of cases, and infections occurred in 84%of cases, which arenot negligible rates (6). Venetoclax is used in combination with chemotherapy and is more widespread at the conventional daily dose of 400 mg.Few reports, in contrast, have been published on the use of venetoclax monotherapy for the treatment of MDS/AML (7), and even fewer studies have been published on the use of this molecule as a monotherapy in the salvage treatment of a "chimeric" entity with simultaneous myeloid and lymphoid presentation (8).In our patient, venetoclax had a "cluster weapon" effect as it induced a double therapeutic response: myeloid and lymphoid responses, including molecular (MYD88) for Waldenström's disease. The mechanism underlying this process has yet to be elucidated. We assume that the response can be explainedby the fact that the treatment was administered as a front-line therapy when the patients were likely more sensitive and had a favourable DDX41 mutation profile (9) (10).

The progression of myelodysplastic syndrome (MDS), which is an entity characterized by often-indolent cytopenias, to acute myeloid leukaemia (AML) is a common and dreaded event. The treatment of this disease in elderly patients, who account forthe majority of patients, is restricted due to comorbidities. In contrast, the evolution of monoclonal gammopathy of undetermined significance (MGUS) or monoclonal B-cell lymphocytosis (MBL) to multiple myeloma (MM) or B-cell lymphoproliferative syndrome (LPS) rarely occurs. However, the co-occurrence of myelodysplastic syndrome and MGUS has been poorly described, and the simultaneous progression

of both diseases is even less common. The treatment of these types of chimeric entities is often the subject of an "empirical" decision by the haematologist oncologist. The decision to treat must take into account not only the risks and benefits but also the costs and accessibility of treatments, first within the medical team and then imperatively with the patient. Due to the emergence of new therapies, chimeric pathologiesare no longer considered an unbeatable two-headed monster.

REFERENCES

1. Hideki Makishima, Ryunosuke Saiki , Yasuhito Nannya , *et al* Germline DDX41 mutations define a unique subtype of myeloid neoplasms *Blood***2023** Feb 2;141(5):534-549.
2. Maitre Elsa,Troussard Xavier Monoclonal B-cell lymphocytosis *Best Practice & Research Clinical Haematology*Volume 32, Issue 3, September **2019**, Pages 229-238
3. Arber D., Orazi A., Hasserjian R. *Etal* International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data *Blood***2022** Sep 15;140(11):1200-1228.
4. Jorge J Castillo, MD Ranjana H Advani MD, Andrew R BranaganMD*etal*Consensustreatmentrecommendations from the tenth International Workshop for Waldenström Macroglobulinaemia *Lancet Haematol*. **2020** Nov;7(11):e827-e837
5. DiNardo, C.D.; Pratz, K. ; Pullarkat, V. *et al*. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. *Blood*. **2019**;133(1):7-17.
6. Keith W Pratz, Brian A Jonas, Vinod Pullarkat*et al* Long-term follow-up of VIALE-A: Venetoclax and azacitidine in chemotherapy-ineligible untreated acute myeloid leukemia*Am J Hematol* . **2024** Apr;99(4):615-624.
7. Konopleva M. , Pollyea D., Potluri J. *et al* Efficacy and Biological Correlates of Response in a Phase II Study of Venetoclax Monotherapy in Patients with Acute Myelogenous *Leukemia Cancer Discov* . **2016** Oct;6(10):1106-1117.
8. Lei Wang, Na Lin Double remission of chronic lymphocytic leukemia and secondary acute myeloid leukemia after venetoclax monotherapy: A case report *Medicine* (Baltimore) **2021** Feb 12;100(6):e24703.
9. Duployez N., Largeaud L., Duchmann M.*, et al* Prognostic impact of DDX41 germline mutations in intensively treated acute myeloid leukemia patients: an ALFA-FILO study *Blood*. **2022** Aug 18;140(7):756-768.
10. C.D. DiNardo, I.S. Tiong, A. Quaglieri*et al* Molecular patterns of response and treatment failure after frontline venetoclax combinations in older patients with AML *Blood*. **2020** Mar 12;135(11):791-803.

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