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Does it really have to hurt? All-oral treatment for acute myeloid leukemia

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The standard of care for patients diagnosed with acute myeloid leukemia (AML) deemed unfit for intensive chemotherapy (IC) has been set by the VIALE-A trial in 2020.[1] The treatment consists of the combination of the hypomethylating agent (HMA) azacitidine and the bcl-2 inhibitor venetoclax. In guidelines such as the NCCN, the combination of the HMA decitabine with venetoclax may be used in the same manner, based on data generated earlier by DiNardo et al..[2] Appropriate dose and schedule are still a major issue, as the standard schedule of 7 days of azacitidine 75mg/m^2 or 5 days of decitabine 20mg/m^2 combined with 28 days of venetoclax per cycle is definitely no “one size fits all” solution: age, comorbidities and molecular disease characteristics demand individualized strategies.

This dual treatment, however, is generally much better tolerated than the conventional AML treatment with IC, with higher response rates and longer overall survival than HMA monotherapy. This allowed treating patients above 80 and even 90 years of age[3]. One major drawback for these elderly patients, however, is that they spend much of their remaining time in their care facilities. The need of transfusions, infections necessitating i.v. antibiotics or antifungals (due to the disease and treatment side effects), frequent disease evaluations and lastly, the administration of the therapy itself, can lead to more time at the hospital than at home, aptly termed “time toxicity “.[4] And this is where the novel strategy presented by Htut et al. comes into play: In this issue of *Haematologica*, they report the long-term follow-up of oral decitabine/cedazuridine plus venetoclax for older or unfit patients with newly diagnosed AML.[5] The combination of oral decitabine with cedazuridine has the same pharmacologic and pharmacodynamic properties, as well as comparable efficacy, as i.v. decitabine, as demonstrated in the ASCERTAIN trial,

and led to its approval for intermediate- and high-risk MDS and CMMoL in the US and for AML in Europe.[6,7] Bazinet et al. then combined decitabine/cedazuridine with venetoclax in elderly unfit AML patients in a single center phase 2 trial.[8] Patients received decitabine/cedazuridine 35mg/100mg on d1-5 and venetoclax 400mg (from d1 to 21 or 28, depending on blast clearance of the bone marrow on d21). Therapy was administered in 28d cycles for a maximum of 24 cycles or until disease progression. Dose adjustments were allowed from cycle 2 onwards to mitigate toxicity. They reported on 62 AML patients treated at the MD Anderson Cancer Center. 49 of those were newly diagnosed and achieved a CR/CRi rate of 57% and a median overall survival (OS) of 11.5 months with a median follow-up time of 18.3 months. Among these, 10 (20%) had already received HMA monotherapy for antecedent hematologic disease and had a significantly inferior outcome with a median OS of only 3.6 months. The publication also included 13 relapsed/refractory patients, also with significantly poorer outcome (median OS of 7.2 months).

Htut et al. now focused on the long-term outcome of 68 elderly unfit patients with newly diagnosed AML treated at MD Anderson Cancer Center between March 16, 2021 and January 18, 2026. It`s an extended analysis of the Bazinet et al. patients, with more patients added and a longer median follow-up which now reached 32 months. They discriminated between patients without (32) or with (36) antecedent hematologic malignancy, with a median age of 81 (78-84) years and 78 (75-82) years, respectively. Beyond the age of the patients, other high-risk features included a performance status of ECOG ≥2 in more than half of the patients, and recurrent complex karyotype -/+ *TP53* mutations. The median number of cycles was 4 (2-7) and 3 (1-8), respectively. The overall response rate (ORR) was 75% in de novo AML

and 58% in secondary AML patients. The median OS of the whole population was 10.2 months, regarding the 2 subgroups it was 12.7 and 7.2 months, respectively. The 3 defined risk groups of the ELN2024 classification discriminated as expected. There were no special safety signals.

The ORR in the VIALE-A amounts to 73% in the azacitidine + venetoclax arm and is therefore comparable to the 75% presented here; OS, though, was significantly higher at 14.7 months in the long-term evaluation, with a median follow-up of 43.2 months.[9] Possible explanations might be the lower median age in the VIALE-A population (76 years), the lower secondary AML rate of 25% and more favorable molecular and cytogenetic risk factors. Another possible explanation was provided by Dr. Roboz and colleagues in the just recently published data of the ASCERTAIN-V trial. This was a phase 1-2b multicentre trial administering the same schedule as Htut et al..[10] Here, the median OS was 15.5 months (median follow-up 11.2 months) in the 102 patients treated within the phase 2b part of the trial, with a median age of 78 years. This was significantly longer than during the phase 1 and 2a part of this trial. The authors concluded that this was achieved through mitigating treatment-related myelotoxicity. A stringent dose-modification guideline for both agents was used, supporting the concept of an induction phase using full dosage and duration of therapy until blast clearance, and a maintenance phase limiting therapy to reduce myelosuppression, therefore decreasing cytopenia-related complications, and ultimately treatment-related mortality.

The all-oral treatment of elderly unfit AML patients with the combination of decitabine/cedazuridine and venetoclax appears to be as effective as its

counterparts with i.v. or s.c. HMA at inducing remissions and shows comparable OS with appropriate dose modifications beyond cycle 1. The main limitation of the presented data is the single-arm design. Also, detecting other factors like health-related quality of life, hospitalization days and healthcare economics would have been very desirable to know here (as well as in ASCERTAIN-V). This is really where the-all oral treatment can hopefully shine when compared to its i.v. or s.c. companions and will hopefully answer the provocative question in the future: Does it really have to hurt?

References

1. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020;383(7):617-629.

2. DiNardo CD, 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.

3. Madarang E, Lykon J, Zhao W, et al. Venetoclax and hypomethylating agents in octogenarians and nonagenarians with acute myeloid leukemia. Blood Neoplasia. 2024;1(2):100016.

4. Gupta A, Eisenhauer EA, Booth CM. The Time Toxicity of Cancer Treatment. J Clin Oncol. 2022;40(15):1611-1615.

5. Htut TW, Kekedjian J, Short N, et al. Long-term follow-up of oral decitabine/cedazuridine plus venetoclax for older or unfit patients with newly diagnosed acute myeloid leukemia. Haematologica. xxx

6. Garcia-Manero G, McCloskey J, Griffiths EA, et al. Oral decitabine-cedazuridine versus intravenous decitabine for myelodysplastic syndromes and chronic myelomonocytic leukaemia (ASCERTAIN): a registrational, randomised, crossover, pharmacokinetics, phase 3 study. Lancet Haematol. 2024;11(1):e15-e26.

7. Geissler K, Koristek Z, Del Castillo TB, et al. Oral decitabine/cedazuridine versus intravenous decitabine for acute myeloid leukaemia: A randomised, crossover, registration, pharmacokinetics study. Br J Haematol. 2024;205(5):1734-1745.

8. Bazinet A, Garcia-Manero G, Short N, et al. Oral decitabine and cedazuridine plus venetoclax for older or unfit patients with acute myeloid leukaemia: a phase 2 study. Lancet Haematol. 2024;11(4):e276-e286.

9. Pratz KW, Jonas BA, Pullarkat V, et al. Long-term follow-up of VIALE-A: Venetoclax and azacitidine in chemotherapy-ineligible untreated acute myeloid leukemia. Am J Hematol. 2024;99(4):615-624.

10. Roboz GJ, Zeidan AM, Mannis GN, et al. All-Oral Treatment of Newly Diagnosed Acute Myeloid Leukemia. N Engl J Med. 2026;394(21):2107-2116.

Figure legend:

Figure 1: Does it really have to hurt?

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