To live is well but to live well is better: venetoclax combination therapy and quality-of-life in acute myeloid leukemia

The FDA approval of venetoclax in combination with hypomethylating agents (azacitidine or decitabine) or low-dose cytarabine has offered renewed hope for elderly/unfit patients with newly diagnosed acute myeloid leukemia (AML). In the pivotal Phase III VIALE-A and VIALE-C studies, complete response rates were superior with venetoclax combination therapy compared to azacitidine (66% vs 28%), and low-dose cytarabine alone (48% vs 13%); moreover, overall survival was prolonged at 14.7 and 8.4 with venetoclax plus azacitidine and low-dose cytarabine, respectively [1, 2]. Major toxicities included grade 3 or higher thrombocytopenia (45%/45%), neutropenia (42%/47%), and febrile neutropenia (42%/32%) in the respective VIALE-A and C studies [1, 2] additionally, 44% of patients receiving azacitidine plus venetoclax experienced nausea [1]. Since health-related quality of life, particularly physical functioning is generally poor in geriatric patients with AML ineligible for intensive chemotherapy and goals of therapy are palliative [3], a global assessment of the patient's perception of the physical and psychosocial impacts of leukemia-directed therapies is imperative for informed therapeutic decisions.

HEALTH-RELATED QUALITY-OF-LIFE WITH VENETOCLAX COMBINATION THERAPY

According to the recently published health-related quality-of-life analysis by Pratz and colleagues, venetoclax combination therapies have the potential to positively impact symptoms and physical functioning in elderly and/or unfit patients with AML [4]. The particular study presents patient-reported outcomes of AML therapies including decitabine, FLT3 inhibitors (midostaurin/gilteritinib), IDH1/2 inhibitors (ivosidenib/enasidenib) and venetoclax, lack information on patient-reported outcomes. The question remains on whether results from the current study are generalizable to patients treated in routine practice since both VIALE-A and VIALE-C studies, complete response rates were superior with venetoclax combination therapy compared to azacitidine (66% vs 28%), and low-dose cytarabine alone (48% vs 13%); moreover, overall survival was prolonged at 14.7 and 8.4 with venetoclax plus azacitidine and low-dose cytarabine, respectively [1, 2]. Major toxicities included grade 3 or higher thrombocytopenia (45%/45%), neutropenia (42%/47%), and febrile neutropenia (42%/32%) in the respective VIALE-A and C studies [1, 2] additionally, 44% of patients receiving azacitidine plus venetoclax experienced nausea [1]. Since health-related quality of life, particularly physical functioning is generally poor in geriatric patients with AML ineligible for intensive chemotherapy and goals of therapy are palliative [3], a global assessment of the patient's perception of the physical and psychosocial impacts of leukemia-directed therapies is imperative for informed therapeutic decisions.
and C trials were limited to patients over 75 years of age with ECOG performance status ≤ 2. Therefore, these findings require prospective validation in real-world series preferably utilizing AML-specific patient-reported outcome measures. Additional limitations of the study include unreported changes in quality of life since assessments were performed every other cycle (month) and the attrition rate was high beyond earlier cycles of therapy, which deserves attention given the continuous nature of venetoclax-based therapy.

FUTURE CONSIDERATIONS

In summary, venetoclax combination therapy has refreshingly changed the treatment paradigm for elderly/unfit AML by not only adding years to life but also life to years. However, the incorporation of patient-reported outcomes in AML is met with unique challenges, especially with respect to the heterogenous assessment tools utilized, and calls for immediate identification of disease and treatment-specific consensus instrument (Fig. 1) [8]. Furthermore, longitudinal health-related quality of life evaluations should be routinely conducted in clinical practice at optimal time points during and after cessation of treatment in patients with AML receiving venetoclax combination therapy.

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REFERENCES

1. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med. 2020;383:617–29.
2. Wei AH, Montesinos P, Ivanov V, DiNardo CD, Novak J, Laribi K, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. Blood. 2020;135:2137–45.
3. Forsythe A, Kwon CS, Bell T, Smith TA, Arondekar B. Health-related quality of life in acute myeloid leukemia patients not eligible for intensive chemotherapy: results of a systematic literature review. Clinecocommses Res. 2019;11:87–98.
4. Pratz KW, Panayiotidis P, Recher C, Wei X, Jonas BA, Montesinos P, et al. Venetoclax combinations delay the time to deterioration of HRQoL in unfit patients with acute myeloid leukemia. Blood Cancer J. 2022; in press.
5. Loh KP, Abdallah M, Kumar AJ, Neuendorf NR, Dahiya S, Klepin HD. Health-related quality of life and treatment of older adults with acute myeloid leukemia: a young international society of geriatric oncology review paper. Curr Hematol Malig Rep. 2019;14:523–35.
6. Stauder R, Lambert J, Desruol-Allardin S, Savre I, Gaugler L, Stojkov I, et al. Patient-reported outcome measures in studies of myelodysplastic syndromes and acute myeloid leukemia: Literature review and landscape analysis. Eur J Haematol. 2020;104:476–87.
7. Buckley SA, Halpern AB, Othus M, Jimenez-Sahagun D, Walter RB, Lee SJ. Development and validation of the AML-QOL: a quality of life instrument for patients with acute myeloid leukemia. Leuk Lymphoma. 2020;61:1158–67.
8. Buckley SA, Kirtane K, Walter RB, Lee SJ, Lyman GH. Patient-reported outcomes in acute myeloid leukemia: where are we now? Blood Rev. 2018;32:81–7.

AUTHOR CONTRIBUTIONS

NG and AT co-wrote the paper.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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