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Review Article

Post ASH 2022: Acute Myeloid Leukemia

Michael D. Diamantidis[1], George Vassilopoulos[2]

[1]*Thalassemia and Sickle Cell Disease Unit, Department of Hematology, General Hospital of Larissa, Larissa, Greece,*
[2]*University of Thessaly Medical School, Head, Division of Hematology, Larisa University Hospital, Affiliate Investigator, Cell and Gene Therapy Lab, BRFAA Athens, Greece*

ABSTRACT:

Acute Myeloid Leukemia (AML) is a highly heterogeneous disease with molecular and cytogenetic aberrations at diagnosis affecting selection of proper treatment and prognosis. Precision medicine allows an individual approach for each patient, based on specific disease characteristics. However, for many patients, allogeneic hematopoietic stem cell transplantation (HSCT) is the only curing option. There is a lot of ongoing research regarding innovative treatment approaches, especially after the approval of novel drugs in the last years. In this manuscript, we made a selection of the most important developments in the field of AML, presented at the 64th Annual Meeting and Exposition of the American Society of Hematology (ASH), which took place in New Orleans, Louisiana, United States, in December 10-13, 2022.

KEY WORDS: *Acute myeloid leukemia (AML), intensive chemotherapy, high risk disease, Venetoclax, Azacitidine, magrolimab, WHO 2022 Classification, International Consensus Classification (ICC) 2022*

INTRODUCTION

Remarkable progress has been achieved in recent years regarding the better understanding of the genetic landscape and the molecular defects of acute myeloid leukemia (AML). The latter has led to novel classifications, prognostic systems incorporating the genomic data of large series of AML patients with the contribution of bioinformatics and most notably, to the approval of novel agents for treating AML. However, there is an unmet need for solving novel challenges that have emerged.

In this manuscript, we chose the most important abstracts in the field of AML, presented at the 64th Annual Meeting and Exposition of the American Society of Hematology (ASH), which took place in New Orleans, Louisiana, United States, in December 10-13, 2022. Choosing 3 important abstracts out of hundreds of excellent works is a difficult task and reflects our personal opinion. These 3 abstracts were also presented in the 2-day hematology meeting of central Greece entitled 'Novel therapeutic choices in Hematology' in the ASH Highlights AML Session. The meeting took place in Larissa, from 3 to 4 February 2023, under the auspices of the Department of Hematology of the University Hospital of Larissa.

Corresponding author:
Prof. Dr. George Vassilopoulos, MD, PhD
Professor, Hematology, University of Thessaly Medical School
Head, Division of Hematology, Larisa University Hospital
Affiliate Investigator, Cell and Gene Therapy Lab, BRFAA Athens, Greece
Tel.: +30 2413501034, +30 2413501625
e-mail: gvasilop@uth.gr, gvasilop@icloud.com

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Oral Abstract 61: AZA/VEN/MAGRO, Phase I/II for high-risk AML

Daver N, Senapati J, Maiti A, Loghavi S, Kadia TM, DiNardo CD, Pemmaraju N, Jabbour E, Montalban-Bravo G, Tang G, Sasaki K, Borthakur G, Yilmaz M, Alvarez J, Pierce SA, Nogueras González GM, Ning J, Issa GC, Andreeff M, Abbas HA, Ravandi F, Garcia-Manero G, Kantarjian H. Phase I/II Study of Azacitidine (AZA) with

Venetoclax (VEN) and Magrolimab (Magro) in Patients (pts) with Newly Diagnosed (ND) Older/Unfit or High-Risk Acute Myeloid Leukemia (AML) and Relapsed/Refractory (R/R) AML. Blood 2022; 140 (Supplement 1): 141-144, doi: 10.1182/blood-2022-170188, ASH 2022; Oral Abstract #61

The combination of azacitidine (AZA) plus venetoclax (VEN) in newly diagnosed acute myeloid leukemia (AML) patients who are not candidates for intensive chemotherapy achieves a complete remission (CR/CRi) rate of 65-70%. Most of these patients relapse almost 2 years after the initial diagnosis with a median overall survival (OS) of 6 months for relapsed patients.[1] In particular, *TP53* AML is one of the most aggressive types of the disease with an extremely poor outcome, as median OS is 5-7 months, even though 30-45% of the patients achieve CR/CRi. There is also debate whether AML patients harboring *TP53* mutation should be transplanted or not. The 3-year OS for *TP53* AML patients who underwent allogeneic hematopoietic stem cell transplantation (HSCT) is only 10%.[2]

Thus, there is an unmet need for novel therapies for these aggressive leukemias, especially in the setting of frail AML patients. CD47 is a molecule expressed at low levels on many normal cells including red blood cells (RBCs) and platelets. Cancer cells express CD47 at higher levels and send a 'don't eat me' signal through the receptor SIRPα (CD47- SIRPα axis) to macrophages and other immune cells, evading the immune surveillance of the host. Magrolimab is a humanized, monoclonal antibody (mAb) with immunomodulatory and antineoplastic properties, targeting CD47 (anti-CD47 antibody), blocking the aforementioned axis and stimulating phagocytosis of cancer cells by macrophages. Conversely, normal cells do not express such signals and are not affected by anti-CD47 mAbs. Hence, magrolimab is a promising therapy tested in clinical trials in several clinical settings in combination with other drugs.[3,4]

Magrolimab plus AZA achieves an overall response rate (ORR) of 49%, a CR of 33% and a median OS of 10.8 months in *TP53* AML patients, whereas the same combination shows a much better efficacy, when applied to non-*TP53* AML: (ORR: 63%, CR: 42%, median OS: 18.9 months). Regardless of the presence or not of *TP53* mutation, the triple combination of AZA plus VEN plus magrolimab has been reported to induce increased phagocytosis in AML cell lines plus improved survival rates in xenograft models from AML patients.[5]

The efficacy and toxicity of AZA plus VEN plus magrolimab in the frontline setting (*de novo* and secondary AML), along with the relapsed/refractory (R/R) AML has been evaluated in a multicohort, non randomized, single arm, phase Ib/II clinical trial (NCT04435691). All R/R AML patients were either VEN naïve or they had prior exposure to VEN. The inclusion criteria for all patients involved an ECOG performance status (PS) ≤ 2, an adequate organ function and white blood cells (WBCs) ≤ 15 x 10^9/L. Moreover, additional criteria were an age of ≥ 75 years or an age of ≤ 75 years plus ineligibility for intensive chemotherapy or ≥ 18 years with *TP53* mutation or adverse-risk cytogenetics, regardless of PS. The majority of the patients studied consisted of a very high AML population risk (frontline: adverse risk 91% - ELN 2017).[6,7]

Primary endpoints of the study were the maximum tolerated dose (MTD), the recommended phase 2 dose (RP2D) and the CR/CRi. Secondary endpoints were the ORR, the duration of response (DOR), the event free survival (EFS), the OS, the measurable residual disease (MRD) negative rate, the 4- and 8- week mortality and the HSCT.

The scheduled cycles were 3, lasting 28 days each. AZA dose was 75 mg/m^2, subcutaneously, on days 1-7 of each cycle. VEN dose was 400 mg per os, from day 1 until day 21 of each 28-day schedule, with a 7-day gap for each cycle (day 22 – day 28). An increased intravenous dose was scheduled for magrolimab for the first cycle, while a stable dose of 30 mg/kg was administered for cycles 2 (4 infusions, days 1, 8, 15, 22) and 3 (2 infusions, days 1, 15). 6 infusions for magrolimab was the protocol for cycle 1: days 1 and 4 with a low dose of 1 mg/kg, day 8 with a gradual increase to 15 mg/kg and days 11, 15 and 22 with the final dose of 30 mg/kg.[7]

The results of the triple combination seem promising for the adverse-risk AML patients. With this combination, patients with *TP53* AML have a CR/CRi of 63%, while these with non-*TP53* adverse AML show a CR/CRi of 88%. In the frontline *de novo* AML cohort with a median follow-up (FU) of 14.5 months, 53% of the patients harboring *TP53* mutation are still alive at 12 months, while 52% of the *TP53* AMLs have not relapsed at 18 months. The relevant rates are much better for wild type *TP53* AMLs, despite the adverse risk: 83% of these patients are still alive at 12 months, whereas 74% of the non-*TP53* AMLs have not relapsed at 18 months with the triple combination. Furthermore, in the frontline secondary AML cohort with a median follow-up (FU) of 14 months, the median OS is only 7.6 months for *TP53* AML patients and 9.6 months for wild type *TP53* AMLs.[7] Secondary AMLs have a much worse prognosis and survival rates compared to *de novo* adverse AMLs.

For the comparison of the triple regimen AZA/VEN/Magrolimab (AVM) vs hypomethylating agents (HMA/VEN), historical cohorts of MD Anderson were used for an indirect retrospective evaluation with the known restrictions, as a head to head assessment under a randomized clinical trial is lacking. Median OS was 10.4 months for AVM vs only 3.5 months for HMA/VEN in matched analysis for *TP53* AML. Since there is a small number of patients with a short FU for *TP53* AML plus a lack of sta-

tistical analysis for *TP53* wild type AML (due to extremely few patients in this subset), no definite conclusions can be drawn. However, based on the abovementioned data, there is a tendency to assume that the addition of magrolimab to VEN/AZA in frontline *TP53* AML patients improves median OS.[7]

Regarding safety of the AVM regimen in AML patients, adverse events (AEs) of grade ≥ 3 were common and well treated. Febrile neutropenia and lung infections were the most frequent, whereas 23% had grade ≥ 3 anemia and 4% grade ≥ 3 infusion reactions. No treatment discontinuation due to the regimen, no life-threatening events or deaths and no immunologic AEs were observed. Nevertheless, 90% had at least 1 manageable grade ≥ 3 AE.

A cautious observation of hemoglobin before magrolimab administration is essential for days 1-10 of cycle 1. The results of AVM are poor in R/R AML (VEN naïve: median OS 5.6 months, VEN exposed: median OS 3.1 months). However, encouraging data emerge in the frontline setting in *TP53* AML. Patients who managed to undergo HSCT had a median OS of 16.6 months, compared to 9.8 months for those who were ineligible for HSCT. Further clinical studies are necessary. The ENHANCE-2 study (NCT04778397) is a randomized, phase III study to evaluate the combination of AZA plus magrolimab vs AZA-VEN or intensive chemotherapy in *TP53* AML. In addition, the randomized, phase III, placebo-controlled study ENHANCE-3 (NCT05079230) will compare AVM vs AZA-VEN in the frontline setting in older or unfit patients.

Oral Abstract 222: 7 days of VEN, instead of 28

Willekens C, Chraibi S, Decroocq J, Carpentier B, Lebon D, Bonnet S, Gauthier N, Pagès A, Dragani M, Khalife-Hachem S, Micol JB, Pasquier F, Wickenhauser S, Saada V, Vergé V, Arbab A, Marzac C, Pascal L, Roos-Weil D, Jourdan E, Bouscary D, de Botton S. Reduced Venetoclax Exposition to Seven Days of Azacitidine is Efficient in Treatment-Naive Patients with Acute Myeloid Leukemia. Blood 2022; 140 (Supplement 1): 537-538, doi: 10.1182/blood-2022-165464, ASH 2022; Oral Abstract #222

The VIALE-A study evaluated the efficacy and toxicity of the combination VEN-AZA to newly diagnosed patients with AML, not eligible for intensive chemotherapy. The ORR (CR/CRi) was 66%, the median OS 14.7 months and the median EFS 9.8 months. This protocol is toxic, as proven by the rates of febrile neutropenia of grade III/IV (42%), grade IV cytopenia after remission lasting >7 days (87%) and deaths not related to disease progression (47.8%). Reduced administration of VEN to 21 days instead of the initially defined 28 days by the protocol does not affect OS.[1,8]

An interesting retrospective study was conducted in France, aiming in reducing the days of VEN administration to 7, instead of 28 (VIALE-A protocol) in the frontline treatment of AML patients not eligible for intensive chemotherapy. 7 centres participated and the patients also received AZA for 7 days (days 1-7 of each cycle), along with the 7-day VEN exposure.[9]

82 patients participated in this retrospective study with a median age of 75 years, similar to that of the VIALE-A study. Many frail and adverse risk AML patients were included, as expected (*de novo* and secondary AMLs). There was enrichment in therapy-related AMLs (32%). The ineligibility to intensive chemotherapy for ages < 75 years was mainly related to prior or concomitant Neoplasia (47%). Moreover, 29% had comorbidities, defined as exclusion criteria in the VIALE-A study.[9] Based on cytogenetics (monosomy 7, complex karyotype), 33 of the patients were poor risk, whereas 70% were classified as adverse risk (ELN 2022)[10], with 21.4% harboring *TP53* mutation.

Regarding the results, 56 patients (68%) achieved CR/CRi, compared to the ORR of the VIALE-A study (66%).[1] The median number of administered cycles was 4 (1-28) with a median FU of 4.8 months (0.3-25.8). Interestingly, the median cycle number for reaching a response was 2 (1-4). A better outcome was observed to those who had a normal karyotype, whereas poor prognosis was found for AML patients with a complex karyotype and *TP53* mutation, as expected. The main reasons for VEN discontinuation were treatment failure or AML relapse (63%), toxicity (30%) and others (7%). 39 patients are still receiving VEN in this study, while 43 discontinued the drug.[9]

Even with the 7-day scheme of administering VEN, toxicity was evident. The cycle 1 toxicity (febrile neutropenia: 49%, platelet or erythrocyte transfusion: 88%) was similar to conventional VEN 28-day exposure. The median delay before cycle 2 was 13 days (2-36 days). The observed median delay to neutrophil recovery was 36 days (15-190), while the corresponding median delay to platelet recovery was 31 days (15-174) in CR/CRi patients.

The median OS of the French study was 12.8 months, only 2 months less than the VIALE-A study (14.7 months), while the median EFS was 7.5 months (comparable with that of the VIALE-A (9.8 months). Moreover, 61% of the patients with CR/CRi underwent a further VEN dose reduction (5 days VEN: 97%, VEN 200 mg/day instead of 400 mg/day: 50%, 35 days between cycles: 29%). The estimated median OS for the AML patients still on VEN is 25.8 months.[9]

The known restrictions for the retrospective studies still exist. The median FU is short and longer FU is necessary to assess OS, EFS and toxicity after VEN cycle 2. However, the estimations for OS and EFS are

encouraging and the results until today are promising. A prospective, randomized clinical trial of head-to-head comparison between the 2 schemes (28-day vs 7-day of VEN administration) is necessary, albeit difficult to be conducted.

Oral Abstract 228: Comparison between WHO 2022 and ICC 2022 AML Classifications

Huber S, Baer C, Hutter S, Dicker F, Meggendorfer M, Pohlkamp C, Kern W, Haferlach T, Haferlach C, Hoermann G. AML and MDS Classification According to Who 2022 and International Consensus Classification: Do We Invent a Babylonian Confusion of Languages? Blood 2022; 140 (Supplement 1): 555-556, doi: 10.1182/blood-2022-162326, ASH 2022; Oral Abstract #228

Novel classifications have emerged in the last year for myeloid neoplasms: the 5th World Health Organization (WHO) 2022[11] and the International Consensus Classification (ICC) 2022.[12] An important work was conducted from the MLL Munich Leukemia Laboratory in Munich, Germany. 1451 AML and Myelodysplastic syndrome (MDS) patients were classified with both classifications.[13] This study is very important not only due to the large patient sample, but mainly because it pointed out the differences and the problems of the 2 classifications to the scientific community. Every patient was classified for each one of the 2 classifications. The results of this elegant original work were also published recently in Leukemia.[14] An important review focusing theoretically on the differences between the 2 classifications (WHO vs ICC) has lately been published.[15]

The median age of the patients studied was 71 years (68 for AML, 73 for MDS). 57% were male and 43% female. No therapy related AMLs were included. The morphology, immunophenotype, cytogenetics and an extensive sequencing were used for these classifications. The sequencing techniques involved an amplification-free WGS (median coverage > 100x) plus WTS (50 Mio reads). The analysis used the following variant callers: Pisces, Strelka, Manda and Pindel (BaseSpace, ILMN).[13]

An initial comparison was conducted between WHO 2017 and WHO 2022. Novel KMT2A fusions have been found and incorporated in the novel WHO 2022 category AML with KMT2A-r. Thus, all previous cases of AML with KMT2A-MLLT3 and some of AML with RUNX1, AML with myelodysplasia related changes (AML-MRC), AML-not otherwise specified (AML-NOS) and MDS-EB-2 (WHO 2017) have now been classified as AML with KMT2A-r (WHO 2022). Conversely, due to the abrogation of the category AML with RUNX1 (WHO 2017), these previously classified as such leukemias, have now been classified either as AML with KMT2A-r, or AML with MECOM-r, or AML-myelodysplasia related (AML-MR) or AML defined by differentiation (WHO 2022).[13] AML-MR cases of WHO 2022 were previously classified as AML with RUNX1, or AML-MRC, or AML-NOS (WHO 2017).[14]

AMLs-NOS constitute 13% of the whole leukemic cohort in the WHO 2017, but only 5% of the same cohort (AML defined by differentiation) when WHO 2022 is applied. The latter is due to the incorporation of more molecular and cytogenetic data in the recent classifications, which favor genetics instead of morphology. The majority of AMLs-NOS (WHO 2017) are now classified as AMLs-MR and fewer as AMLs defined by differentiation or AMLs with KMT2A-r (WHO 2022).[13]

Due to changes in the diagnostic criteria, patients classified as MDS, according to the WHO 2022[11] are classified either as MDS or MDS/AML, based on the ICC 2022.[12] Furthermore, cases with AML-MR (WHO 2022) are either classified as AML with mutated *TP53*, or AML with MR gene mutations or AML with MR cytogenetic abnormalities or AML-NOS.[14] Interestingly, as the category AML with mutated *TP53* does not exist in the WHO 2022 classification, such cases with this classification term (ICC 2022) are classified as AML-MR in the WHO 2022, based on co-existing mutations or cytogenetic abnormalities with the *TP53* mutation.[13,14] Finally, there are few cases classified as AML with defining genetic abnormalities (WHO 2022), independent of blast cutoff. The genetic abnormality is necessary and sufficient prerequisite to classify the leukemia in the WHO 2022. However, when the blast count is less than 10%, then the same case is classified as MDS in the ICC 2022 classification, because in the ICC classification, a blastic count ≥ 10% is essential even for specific cytogenetic abnormalities.[12,14]

Both classifications (WHO and ICC 2022) are in favor of a more genetic classification of AML (molecular and cytogenetics), instead of a morphological classification. Nevertheless, differences in the exact diagnostic criteria, lead to a lack of a direct comparison for several subsets of AML patients. The parallel use of 2 different classifications causes confusion in the diagnostic language for clinical and non-clinical doctors, patients and legal authorities. A single, unified, commonly accepted classification by all the scientific community is essential for comparing the diagnostic data and for treatment decisions, inside and outside of clinical trials. Thus, accurate diagnosis and the best treatment option will be provided, along with a better design of clinical trials.

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