review

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ASH 2022—new developments in acute myeloid leukemia

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Summary Recent years have provided progress for the treatment of acute myeloid leukemia (AML) patients by translating insights from basic research on AML biology into new drugs and concepts. The latest developments presented at the 2022 annual meeting of the American Society of Hematology (ASH) are covered in this review, including discussion of new classifications, treatment of elderly unfit patients, and new approaches towards allogeneic transplantation.

Keywords Prognosis · Classification · Elderly Patients · Targeted molecular therapy · Allogeneic transplantation

Introduction

The 2022 annual meeting of the American Society of Hematology (ASH) in New Orleans provided a stage to present and discuss (gratefully face-to-face, but also on virtual platforms) numerous new scientific achievements including the field of acute myeloid leukemia (AML). As there was no single presentation on data forming the basis for immediate transfer into new therapeutic approaches, choice of abstracts for this report was difficult and subjective. Three topics were selected, and an apology needs to be made for those that cannot be mentioned. This review will cover the ongoing discussion on new systems for classification and risk assessment, shed some light on the present standard and future prospects for elderly unfit patients, and finally discuss a potential paradigm shift in stem cell transplantation for AML.

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New classifications and risk assessment proposals—a way out of the confusion?

The year 2022 saw the publication of two different proposals for improved AML classifications by the WHO (World Health Organization) and ICC (International consensus classification) groups [1, 2] as well as an updated ELN (European Leukemia Net) risk classification [3]. Names and definitions for proposed modified and also new entities differ from previous systems—which might provide progress—but also between the proposals, which confers a considerable amount of confusion and impedes comparison of studies and reports. At ASH, several groups attempted to evaluate these proposals. An example is the evaluation of 1451 AML and myelodysplastic syndrome (MDS) patients from the Munich Leukemia Laboratory (MLL) [4]: Besides the new ICC category of MDS/AML, comprising patients with 10–19% bone marrow blasts ($n=137$), the proportion of AML (WHO $n=746$) and MDS (WHO $n=705$) remains relatively unchanged. Only a small number of patients (~1%) will be differently classified as AML or MDS based on the phrasing of the definitions. For WHO 2022 vs WHO 2016, the percentage of genetically defined patients remains relatively unchanged at about 65%, albeit with a new composition due to new (*KMT2A, MECOM, NUP98*, "other") and abandoned (*RUNX1*) genetic definitions. The proportion of patients with MDS-associated genetic changes now termed "AML-myelodysplasia related" by WHO 2022 increases from 22% to 28%, and of only morphologically defined subtypes decreases from 13% to 5%. The authors concluded that basic concepts of classification are similar between WHO 2022 and ICC, both emphasizing the genetic basis for definitions. Unfortunately, differences in the exact diagnostic criteria lead to non-comparable diagnoses in a subset of patients. As it is,

use of two different classifications in parallel carries an inherent risk for patients, physicians, and clinical researchers. Formulation of a unified commonly accepted classification is an important goal for the near future. This should re-establish data comparability for use in routine and research clinical settings.

Risk assessment has also seen modification in 2022. Major changes in the new ELN risk classification are the exclusion of the *FLT3-ITD* allelic ratio, modification of the consideration of the context of NPM1 mutations, categorization of in-frame mutations affecting *bZIP* of *CEBPα* regardless of monoallelic or biallelic as favorable risk and finally inclusion of myelodysplasia-related gene mutations within the adverse risk group; mutations in IDH1/2 or DNMT3A are still not classified [3]. A comparison of old and new ELN risk criteria was performed in 624 AML patients undergoing standard chemotherapy induction and consolidation, yielding a CR rate of 83.3% and a rate of allogeneic transplant of 44.9% [5]. In all, 134 patients were reclassified; each of the risk groups had a significant prognostic difference for overall survival (OS; $P < 0.001$) and event-free survival (EFS; $P < 0.001$). The authors concluded that the ELN 2022 guideline was superior to the ELN 2017 for risk stratification and better predicted the prognosis of patients with AML in the real world.

It is important to apply classification and risk assessment systems to patients that are comparable to those from which the systems were derived from, especially in terms of treatment. This crucial point was emphasized by an exploratory post hoc analysis on predictive markers including the ELN risk criteria for outcomes of patients treated with venetoclax and azacitidine in the pivotal phase 1b and III trials. ELN risk groups, based on younger patients who received IC, are not prognostic in patients receiving venetoclax plus azacitidine; there was little OS distinction between favorable and intermediate risk groups, whereas the adverse risk ELN groups could be further refined. Mutational status of four genes (*FLT3-ITD, KRAS, NRAS*, and *TP53*) yielded higher prognostic power. Three prognostic risk signatures indicate higher benefit, intermediate benefit, and lower benefit [6].

As many patients with *NPM1* mutations carry at least three gene mutations, further refinement by including the prognostic values of these co-mutations could be helpful, machine learning was used to provide further insight. Researchers from the European Harmony Alliance analyzed co-mutational pattern in 1093 intensively treated adult patients with *NPM1*-mutated AML [7].

FLT3-ITD+ DNMT3A as co-mutation was associated with adverse prognosis (2-year OS 33%, similar to TP53 mutated), whereas *FLT3-ITD+IDH* co-mutations in the absence of *DNMT3A* mutation had an excellent prognosis (2-year OS 80%), *IDH+ DNMT3A* co-mutations decreased OS toward intermediate risk (2-year OS 59%). A decision tree including additional parameters as a practical tool was proposed.

Common baseline of the discussion on classification and risk assessment was the hope and expectation that the future will see further refinement and improvement in hopefully unified generally applicable tools.

Update of venetoclax + azacitidine and future prospects

For the phase 3 VIALE-A trial (azacitidine plus venetoclax or placebo) that established the present standard first-line treatment for elderly unfit AML patients, long-term follow-up data with two additional years of follow-up including a 100% OS analysis were presented [8]: toxicity and efficacy data were confirmed. Due to toxicity, venetoclax duration was reduced in responders to ≤ 21 days in 76%, and cycle delays were needed in 91.1%. OS data for the whole population were confirmed with median 14.7 months for the combination versus 9.6 months for azacitidine alone. Duration of CR, CR + CRi, and OS in some subgroups were longer at this 100% OS analysis than at the 75% OS analysis: with azacitidine plus venetoclax, median OS for patients with MRD < 10^{-3} was 34.2 months, and median OS for patients with *IDH 1/2* mutations was 19.9 months. In conclusion, these data confirmed the long-term survival benefit for patients treated with azacitidine plus venetoclax.

As this combination is associated with considerable toxicity—especially hematotoxicity—a retrospective study by French hematologists evaluating reduced intensity for this protocol limiting venetoclax exposure to 7 days per cycle is of interest [9]: the authors reported 82 treatment-naïve patients of which 29.3% had comorbidities defined as exclusion criteria in the VIALE-A study. Reporting lower toxicity, overall OS was shorter compared to the VIALE-A results, although for those patients that might have been included in VIALE-A a comparable OS of 13.8 months was found. Obvious limitations are lower patient numbers and the study design, but this concept merits further exploration in randomized trials.

Ongoing further trials focus on triplet therapies including venetoclax and azacitidine or the combination of chemotherapy with venetoclax:

In younger first-line patients, venetoclax combined with cladribine, idarubicin, cytarabine (CLIA) as induction therapy is being tested yielding high response rates albeit associated with considerable toxicity [10]. The phase 1b CAVEAT study for elderly patients (median age 71) was updated at ASH [11]: Here, shorter venetoclax administration is combined with a modified 2 + 5 protocol. CR rate was 73% (for de novo AML 90%) and median OS 15.4 months (31.3 months for de novo patients) — a randomized trial is planned.

For relapsed/refractory patients, an update on the phase IIb study of venetoclax with FLAG-IDA (median

2 cycles) was presented [12]. Compared to historical controls of FLAG-IDA alone ORR (60%) and CRc rate (53%) were improved at the cost of substantial toxicity. Among responding patients, 68% could subsequently undergo allogeneic transplantation. Unfortunately, no effect was seen in *TP53*-mutated patients who still hvae a poor outcome with all available therapies.

Triplets complementing azacitidine plus venetoclax with biologicals could potentially provide additional efficacy without or only low additional toxicity. Combinations discussed at ASH included the anti-CD47 antibody magrolimab or the anti-CD123 conjugate pivekimab sunirine for all-comers and gilteritinib for *FLT3*-mutated patients [13–15]. These phase 1 trials are hypothesis generating but need follow-up for definitive judgements.

Generally, response rates in early trials may not translate into OS benefit within randomized comparison. Examples from the *FLT3*-mutated setting include the Lacewing study testing the combination of azacitidine with gilteritinib [16]. Whereas the combination yielded significantly higher CRc rates, similar OS was observed. Therefore, it remains to be tested whether the doublet venetoclax + gilteritinib that recently reported high mCRc and FLT3 molecular response rates regardless of prior FLT3 inhibitor exposure translates into an OS benefit [17]. Of general interest is the observation that also FLT3 wild-type patients may benefit from FLT3-targeting drugs such as gilteritinib as venetoclax synergizes with gilteritinib and by suppressing MCL-1 decreases venetoclax resistance also in *FLT3* wild-type AML [18].

Paradigm shift for relapsed/refractory AML planned for allogeneic transplantation?

One of the general hot discussion topics at ASH 2022 was related to AML: In the Plenary Session's fourth presentation, results of the ASAP phase III trial were discussed [19]. This study challenges the common concept that complete remission—ideally MRD negative—is prerequisite for a favorable outcome of salvage allogeneic transplantation and that relapsed/refractory AML patients benefit from an attempt to induce CR by intensive chemotherapy. Technically, previous studies had shown that a transplant in aplasia after induction is feasible. In a randomized phase 3 trial, sequential conditioning and immediate allogeneic stem cell transplantation was compared to intensive remission induction chemotherapy followed by allogenic transplant. Relapsed or refractory patients aged 18–75 years, fit for intensive treatment with an HLA compatible donor, could be included. In the remission induction strategy arm (RIST), patients were treated with HAM and subsequent transplant. In the so-called disease control arm (DISC), watchful waiting was recommended, LDAC or single doses mitoxantrone were allowed prior to sequential conditioning and transplant. Primary endpoint was CR at day 56 after transplant; statistical goal was non-inferiority. A total of 281 patients (183 refractory, 98 after relapse) with a median 30% bone marrow blasts were included. In all, 272 were treated per protocol (138 DISC/134 RIST): 24% of DISC patients needed disease-control measures, while 46% of RIST patients achieved CR after HAM. At 24 weeks, 98% and 96% of patients were transplanted (DISC/RIST, respectively), in the RIST arm irrespective of remission status. Median time to transplant was longer with RIST versus DISC—median 8 versus 4 weeks, adverse events and hospitalization rates before transplant were significantly higher with RIST. CR at day 56 after transplant was 84.1% in the DISC and 81.3% in the RIST group ($p = 0.047$), 1-year LFS from CR at day 56, and 1- and 3-year OS were not significantly different. There were no differences by biology; only younger age favored RIST. The authors concluded that salvage with HAM before allogeneic transplant did not result in a higher overall success rate and did not confer a survival advantage. Watchful waiting followed by sequential conditioning and allo-HCT resulted in comparable overall CR rates and survival with fewer days spent in hospital. Morphological CR at time of transplant seemed to be less important than previously perceived and MRD not a prerequisite for outcome. Several limitations and caveats need to be taken into account. Refractory patients were included after a single induction, whereas a second cycle might have led to remission. There is a possible selection bias by including less proliferative disease due to the design of the DISC arm. A variety of conditioning regimens (including RIC) was used limiting comparability. The choice of HAM as salvage regimen can be debated because alternative schemes such as Ida-FLAG which are widely used and novel agents such as venetoclax were not included, thus, limiting generalizability of claims. Finally, the trial was not formally powered for overall survival and longer-term follow-up is needed. Nevertheless, this study has the potential to change practice at least for some patients and is certainly a driver for further studies and analyses. From a logistic point of view, the data stress the need for rapid evaluation of patients and identification of potential donors as time to transplant seems crucial in many settings.

Concluding remarks

Due to limited space many acute myeloid leukemia (AML) topics with potential interest presented at ASH could not be covered. These include papers on classic chemotherapy, immunotherapy, new targeted-treatment approaches, personalized medicine, and also patient-related topics. Commitment for improving AML care for all patients, young and old, fit and unfit is the common thread of all efforts and holds promise for AML future.

Conflict of interest M. Pfeilstöcker: honoraria as speaker and/or consultant: Abbvie, BMS, Jazz, Novartis, Sandoz, Sobi, financial support for scientific projects: BMS.

References

1. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022;36(7):1703–19.
2. Arber DA, Orazi A, Hasserjian RP, et al. International consensus classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200–28.
3. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345–77.
4. Huber S, Baer C, Hutter S, et al. 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):555–6.
5. Song GY, Kim T, Ahn SY, et al. Prognostic predictability of 2022 European Leukemianet (ELN) risk stratification in the real world. Blood. 2022;140(Supplement 1):1018–9.
6. Döhner H, Pratz KW, DiNardo CD, et al. ELN risk stratification is not predictive of outcomes for treatment-naïve patients with acute myeloid leukemia treated with Venetoclax and Azacitidine. Blood. 2022;140(Supplement 1):1441–4.
7. Hernández Sánchez A, Ramiro AV, Strang E, et al. Machine learning allows the identification of new co-mutational patterns with prognostic implications in NPM1 mutated AML—results of the European Harmony Alliance. Blood. 2022;140(Supplement 1):739–42.
8. Pratz KW, Jonas BA, Pullarkat VA, et al. Long-term follow-up of the phase 3 Viale—a clinical trial of Venetoclax plus Azacitidine for patients with untreated acute myeloid leukemia ineligible for intensive chemotherapy. Blood. 2022;140(Supplement 1):529–31.
9. Willekens C, Chraibi S, Decroocq J, et al. Reduced Venetoclax exposition to seven days of Azacitidine is efficient in treatment-naïve patients with acute myeloid leukemia. Blood. 2022;140(Supplement 1):537–8.
10. Reville PK, Kantarjian H, Borthakur G, et al. Venetoclax added to Cladribine (CLAD) + low dose AraC (LDAC) alternating with Azacitidine (AZA) is highly active as frontline therapy in older patients with newly diagnosed acute Myeloid leukemia in a phase 2 study. Blood. 2022;140(Supplement 1):9041–3.
11. Chua CC, Loo S, Reynolds J, et al. High response and prolonged treatment-free remission after a short-course of modified intensive chemotherapy and Venetoclax in elderly AML: an updated analysis of the caveat trial. Blood. 2022;140(Supplement 1):1708–10.
12. Desikan SP, Konopleva M, Takahashi K, et al. Updated phase IIb results of Venetoclax with FLAG-IDA in relapsed or refractory acute myeloid leukemia. Blood. 2022;140(Supplement 1):534–6.
13. Daver N, Senapati J, Maiti A, et al. 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):141–4.
14. Daver N, Montesinos P, Aribi A, et al. Abstr 62 broad activity for the Pivekimab Sunirine (PVEK, IMGN632), Azacitidine, and Venetoclax triplet in high-risk patients with relapsed/refractory acute Myeloid leukemia (AML). Blood. 2022;140(Supplement 1):145–9.
15. Short N, DiNardo CD, Daver N, et al. Updated results from a phase I/II study of the triplet combination of Azacitidine, Venetoclax and Gilteritinib for patients with FLT3-mutated acute Myeloid leukemia. Blood. 2022;140(Supplement 1):2007–9.
16. Wang ES, Montesinos P, Minden MD, et al. Phase 3 trial of gilteritinib plus azacitidine vs azacitidine for newly diagnosed FLT3mut+ AML ineligible for intensive chemotherapy. Blood. 2022;140(17):1845–57.
17. Daver N, Perl AE, Maly J, et al. Venetoclax plus Gilteritinib for FLT3-mutated relapsed/refractory acute Myeloid leukemia. J Clin Oncol. 2022;40(35):4048–59.
18. Janssen M, Schmidt C, Bruch PM, et al. Venetoclax synergizes with gilteritinib in FLT3 wild-type high-risk acute myeloid leukemia by suppressing MCL-1. Blood. 2022;140(24):2594–610.
19. Stelljes M, Middeke JM, Bug G, et al. In patients with relapsed/refractory AML sequential conditioning and immediate allogeneic stem cell transplantation (allo-HCT) results in similar overall and leukemia-free survival compared to intensive remission induction chemotherapy followed by Allo-HCT: results from the randomized phase III ASAP trial. Blood. 2022;140(Supplement 1):9–11.