Updates on Acute Myeloid Leukemia Management in older patients

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Abstract
Acute myeloid leukemia (AML) is the most common type of acute leukemias in adults accounting for 80 percent of cases \cite{1}. While AML is a relatively rare disease, it is more common in older adults, frequently diagnosed among people aged 65–74 with highest death in patients aged 75–84 \cite{2}. Survival of patients with AML is heterogeneous and depends on several factors: (1) Patient related factors including performance status, comorbidities, along with diversities in leukemia subtype and characteristics (near gene sequencing, cytogenetics). Herein we have tried to focus on this specific age group and describe different treatment options (chemotherapy, immune checkpoint inhibitors, Bispecific T-cell engagers (BiTES), Chimeric Antigen Receptor T-cell Therapies (CAR-T), and Allogeneic Hematopoietic Stem Cell Transplantation) based on the available studies and ongoing clinical trials preliminary results.

Introduction
Acute Myeloid Leukemia (AML) is the most common type of acute leukemias in adults accounting for 80 percent of cases \cite{1}. While AML is a relatively rare disease, it is more common in older adults, frequently diagnosed among people aged 65–74 with highest death in patients aged 75–84 \cite{2}. Survival of patients with AML is heterogeneous and depends on several factors: (1) Patient related factors including performance status, Co-morbidities and organ function, (2) Disease related factors including type of AML (de novo Vs. Secondary), cytogenetics and molecular markers impacting outcomes \cite{1,3,4}.

To better assess the prognosis of patients with AML, based on cytogenetics and molecular markers, the European Leukemia Net (ELN) proposed a system that identifies three prognostic risk groups that differ based on the rates of complete remission (CR), disease-free survival (DFS), and overall survival (OS) in the hopes of identifying potential new avenues of treatment for these heterogeneous disease entities \cite{5}.

Older Adults with AML (OA-AML) have worse survival than younger cohorts \cite{6,7}. In a report from the Swedish Acute Leukemia Registry, early death rates in ≥70 years old patients were five times more than those of <50 years old with 5-year overall survival (OS) of <10% among patients ≥70 years old vs. 55% among those <50 years old; ECOG greater than 2 or having significant co-morbid conditions have been associated with worse outcome \cite{8}. Adverse cytogenetics (i.e., loss of 5q, 7q, and 17p, monosomal karyotype and complex karyotypes) is another important factor which occurs more frequently in older patients leading to higher relapse rate and inferior outcomes compare with younger patients \cite{9-11}.

OA-AML have a higher frequency of mutations in genes known to be poor prognostic predictors \cite{12,13}. For example, mutations of DNMT3A are reported in up to a third of OA-AML cases \cite{14-16}. TP53 mutations along with complex karyotype (CK) leads to dismal outcomes; with 3-year estimated EFS of 1% versus 13% (log-rank, P = 0.0007); RFS (relapse free survival) of 7% versus 30% (P = 0.01); and OS of 3% vs. 28% (P < 0.0001), after induction chemotherapy for CK/TP53 mutated and CK/TP53 wild-type patients respectively \cite{17}. While hypomethylating agents and venetoclax seem to have improved results, TP53 mutated patients still suffer worse outcomes than WT \cite{18}. Lastly, Other mutations such as ones seen in as IDH1/2, ASXL1, RUNX1, TET2, and BCOR also negatively affect outcomes in OA-AML \cite{13,19}.

Treatment
Traditionally, AML is treated with induction chemotherapy and depending on the risk category followed by consolidation with chemotherapy or Allogeneic hematopoietic cell transplantation (alloHCT). Unfortunately, data on the best choice of therapy in OA-AML is sparse as several variables need to be considered before deciding which pathway to be used. Geriatric assessment (GA) should consist of a comprehensive evaluation of the patient’s general functional status, falls, comorbidities, including psychological conditions, cognition, and treatment outcomes. Herein we have tried to focus on this specific age group and describe different treatment options (chemotherapy, immune checkpoint inhibitors, Bispecific T-cell engagers (BiTES), Chimeric Antigen Receptor T-cell Therapies (CAR-T), and Allogeneic Hematopoietic Stem Cell Transplantation) based on the available studies and ongoing clinical trials preliminary results.

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social support, and nutritional status. GA has been studied specifically in OA-AML, showing ability to better predict prognosis and potentially improving outcomes [20–22].

Chemotherapy

Intensive chemotherapy (IC)

The standard of care for the induction of AML remains cytarabine 200 mg/m²/continuous infusion x 7 days with daunorubicin 60 or 90 mg/m² or Idarubicin 12 mg/m² x 3 days (7+3) first described in the 1970s [23,24]. Traditionally OA-AML treated with 7+3 had worse outcomes. In a retrospective analysis of 968 adults with previously untreated AML, which investigated 3 clinical trials from Southwest Oncology Group (SWOG) [25–27], OA-AML treated with 7+3 presented with poorer performance status, multidrug resistance (57%) and unfavorable cytogenetics in 51% of patients older than 75. Additionally, OA-AML had a CR rate of 33%, median OS of 3.5 months, and DFS of 8.9 months, while young patients had a CR rate of 64%, median OS 18.8 months, and DFS of 21.6 months regardless the presence of favorable cytogenetics [9]. In the AML-14 trial, a total of 1273 patients were recruited addressed different dose regimens for Daunorubicin and Cytarabine in addition to the multidrug resistance modulator PSC-833 in a 1:1 randomization in patients predominantly aged over 60 years with AML and High-Risk MDS. The study showed an overall response rate (ORR) of 62% (complete remission (CR) 54%, complete remission without platelet/neutrophil recovery (CRi) 8%), with 5-year survival rate of 12% without improving outcomes in older patients [28]. In 2009, 813 patients older than 60 years of age were randomized to escalated-dose of daunorubicin (90 mg/m²) Vs. conventional dose (45 mg/m²), leading to higher rates of complete remission (73% vs. 51%), event-free survival (29% vs. 14%), and overall survival (38% vs. 23%) when compared to the conventional dose regimen, without additional toxic effects [29].

Fortunately, over the past decades, a wave of novel arsenal of various therapies has drastically altered the treatment landscape of AML, especially in the elderly. One such therapy is Vyxeos (CPX-351) which is a liposomal formulation of daunorubicin and cytarabine that releases the drugs in a fixed 5:1 molar ratio and was examined in a randomized phase II study on patients age 60 to 75 years with newly diagnosed AML, first-line CPX-351 showed a trend to higher response rates (66.7% vs. 51.2%, P = .07), improved 60-day mortality (4.7% vs. 14.6%) with OS (12.1 vs. 6.1 months; HR = 0.46, P = .01) in sAML subset when compared to 7+3 [30]. Based on these results, an open-label, randomized, phase III trial enrolled 309 elderly patients with newly diagnosed high-risk or sAML received one to two induction cycles of CPX-351 7+3 followed by consolidation therapy. This trial showed that CPX-351 – 7+3 significantly improved median OS (9.56 vs 5.95 months; P = 0.003) and ORR (Overall Response Rate) (47.7% vs 33.3%; two-sided P = .016), with improved outcomes observed across age-groups and AML subtypes [31]. These studies ultimately led to the approval by the FDA in 2017 of CPX-351 for the treatment of adults with newly diagnosed AML with myelodysplasia-related changes (AML-MRC) or therapy-related acute myeloid leukemia (t-AML). The 5-year follow-up results from the phase 3 study demonstrated persistent improved OS with CPX-351 vs. 7+3 chemotherapy in the overall study population, but the survival rates were still dismal (21% vs. 9% and 18% vs. 8%) at 3 and 5 years, respectively in both groups respectively [32].

Aspacytarabine (BST-236) is a novel cytarabine prodrug designed to reduced toxicity by decreasing the peak exposure of free cytarabine in unfit patients. The phase 1/2 and phase 2 studies involving 42 AML patients with a median age of 73 years. Forty-three percent of patients with adverse cytogenetics attained CR, with median OS for sAML group of 6.8 months, not reached for the de novo AML patients with good safety profile with a 30-day mortality rate of 7%. [33].

Hypomethylating agents

Hypomethylating agents have also emerged as therapeutic alternatives in OA-AML management. Decitabine (DEC) and Azacytidine (AZA) have been evaluated in this patient population. The DACO-016 study reported the efficacy and safety of decitabine vs. treatment choice (TC; supportive care or cytarabine) in 485 older patients with newly diagnosed AML with the median age of 73 years old. The primary analysis with 396 deaths (81.6%) showed a nonsignificant increase in median OS with decitabine (7.7 months; 95% CI, 6.2 to 9.2) versus TC (5.0 months; 95% CI, 4.3 to 6.3; P = .108; hazard ratio [HR], 0.85; 95% CI, 0.69 to 1.04). The CR / CRi rate was 17.8% with decitabine versus 7.8% with TC (odds ratio, 2.5; 95% CI, 1.4 to 4.8; P = .001), and the adverse events were similar between the two groups [34]. These findings led to the approval in Europe of Decitabine for patients aged ≥ 65 years with de novo/secondary AML who are ineligible for intensive therapy. The AZA-AML-001 trial was a multicenter, randomized, open-label, phase 3 study that evaluated efficacy and safety of AZA vs. conventional care regimens (CCRs; standard induction chemotherapy, L-DAC, or supportive care only) in 488 elderly patients with newly diagnosed AML and >30% bone marrow blasts. The median OS with AZA was 10.4 months (95% confidence interval [CI], 8.0–12.7 months) vs 6.5 months in the CCR group (95% CI, 5.0–8.6 months) with a hazard ratio of 0.85 (95% CI, 0.69–1.03; stratified log-rank P = .1090). Additionally, the one-year survival estimate of 50.7% in AZA compare to 33.8 in CCR (difference, 16.9%; 95% CI, 1.5%, 32.1%) put AZA as a valid treatment option for this difficult-to-treat AML population [35]. Moreover, a recent report from the Pethema registry found no significant differences in ORR, CR/CRi, or OS between DEC and AZA [36]. HMA have been used in combination with chemotherapy also. One such combination is low dose cytarabine (LDAC) alternating with clorarabine and decitabine. In 2015, Kadia, et al. reported a phase 2 study using this regimen in 180 elderly patients with an ORR of 68% and a CR of 60%. The median OS was 11.1 months for all patients and 18.5 months for those achieving CR/CRi with four and eight-week mortality rates of 3% and 7%, respectively [37]. This same group in 2018 reported their experience with LDAC in combination with Cladribine alternating with decitabine on 118 patients with 58% CR rate, median OS of 13.8 months and DFS of 10.8 months. Similar to clorarabine study, the four and eight-week mortality rates were 1% and 7%, respectively [38]. Targeted agents have also been successfully used in combinations with these agents, as explained below.

BCL-2 Inhibitors

Venetoclax (VEN) is now considered as category 1 recommendation in combination with HMA in ELP who cannot tolerate high-dose chemotherapy regimen[39]. VEN is a BCL-2 inhibitor on the leukemic cells which are dependent on MCL-1 for their survival [40–42]. The effectiveness of VEN monotherapy was reported in a phase 2 single-arm study of 32 patients with high-risk relapsed/refractory AML (RR AML) or in those who were unfit to receive intensive chemotherapy. The ORR was 19%, with an additional 19% of patients demonstrated antileukemic activity not meeting IWG criteria [43]. Based on these results and the synergistic activity observed in preclinical data, combinations therapies were studied. DiNardo, et al. reported the combination of VEN and HMA, a phase 1b study of 57 elderly patients who were ineligible for standard induction, demonstrated ORR of 75% (95% CI 62.2–85.9)
with 61% of patients achieving CR/CRi regardless of HMA type. The median duration of response (mDOR) was 8.4 months, with a median OS of 12.3 months [44]. These results were confirmed by the VIAL-E-A phase 3 trial which 431 OA-AML (median age 76 years, range 49-91) were randomly assigned to AZA plus VENVE (AZA/VEN) or placebo. After a median follow-up of 20.5 months, the CR/Cri and median OS were 66.4% vs. 28.3% (P<0.001) and 14.7 vs. 9.6 months (HR for death, 0.66; 95% CI, 0.52 to 0.85; P<0.001) in the AZA/VEN and control groups, respectively; additionally, mortality rate at 30 day remained similar in two groups (7% Vs. 6%) [45]. Compared to intensive chemotherapy (IC), decitabine combined with VEN (DEC/VEN) has also shown better outcomes; Maiti, et al. reported a propensity score-matched analysis stratified by risk of treatment-related mortality of 85 older adults with median age of 72 years (range 63-89). After a median follow-up of 12.4 months in DV and 81.2 months in the IC cohort, they found a significantly higher CR/Cri of 81% vs. 52% (P <0.001), with a longer OS of 12.4 vs. 4.5 months, respectively (HR = 0.48, 95%CI 0.29-0.79, P <0.01) [46].

VEN also has been combined with other agents to try improving outcomes. VEN plus low dose cytarabine (VEV-LDAC) was studied in a phase 3 randomized placebo-controlled trial of 211 patients (2:1) with median age of 76 years (range 36-93) and after a median follow up of 18 months, the median OS was 8.4 months (95% CI, 5.9-10.1) for V-LDAC vs 4.1 months (95% CI, 3.1-8.1) for those receiving placebo with an overall response rate of 48% versus 13% (P < 0.001), and a CR rate of 27% versus 7% (P < 0.001) respectively [47]. Other chemotherapy combination regimens have also been successful, but they have not been studied in the elderly [48,49]. Isocitrate dehydrogenase (IDH1/2) mutations have been shown to cause increased leukemia cell sensitivity to VEN likely related to inhibition of cytochrome c oxidase in the electron transport chain, thus lowering the threshold for triggering VEN induced apoptosis [50]. This synergism was confirmed clinically on the phase II monotherapy (VEN-VEN) study, which found increased activity in patients with AML treated with VEN who harbored IDH1/2 mutations, with a third of them achieving CR/Cri [43]. Similar findings were reported in those patients treated with V-LDAC [51]. Lachowiez, et al. in 2020 reported the results of a phase Ib/2 study ofivosidenib (IVOSI) with VEN +/- A AZA in 19 patients with IDH1-mutated hematologic malignancies; seventeen patients had AML, with a median age of 68 years. In 18 evaluable patients, the composite complete remission (CRc, CR+Cri+CRh) rates was 78% (treatment-naive: 100%, R/R: 75%) with a median time to best response of 2 months. After a median follow-up of 3.5 months, in treatment naive patients, median OS was not reached (9.7 months in R/R patients) [52]. FLT3 inhibitors are another group of agents under investigation in addition to VEN for the management of AML. In a recently reported phase 1B study, Daver, et al. investigated the safety and efficacy of VEN combined with Gilteritinib for 39 patients with RR FLT3 mutated AML. While not specifically looking into just an elderly population, the average age of the population was 63 years. it was found a modified composite CR (CR + CRp + CRi) of 83% but due to the short follow-up of a large number of recently enrolled patients, the interpretation is limited [53].

**Isocitrate Dehydrogenase 1 and 2 Inhibitors**

Recurrent mutations in IDH1 and IDH2 produced 2-hydroxyglutarate (2HG) from α-KG, preventing the histone demethylation leading to a block in differentiation and leukemogenesis [54,55]. IVOSI and Enasidenib (ENASI) are oral IDH1 and IDH2 inhibitors which have been approved as monotherapies for RR AML; A phase 1, multicenter, open-label study treated 60 patients with IVOSI plus induction chemotherapy and 93 patients with ENASI plus induction chemotherapy with the median age of 62.5 and 63 years in the IVOSI and ENASI cohorts, respectively. The CR/Cri/CRp at the end of induction was 72%, and 63% with IVOSI and ENASI, respectively. After a follow-up of 9.3 and 14.5 months, median OS was not reached and 14.5 with 12-months survival of 78% and 76% in both IVOSI and ENASI treated cohorts; respectively [56]. The HOVON150 AML trial (NCT03839771) is a phase 3, multicenter, double-blind, randomized, placebo-controlled study of IVOSI or ENASI in combination with induction therapy and consolidation therapy followed by maintenance therapy currently recruiting patients with newly diagnosed AML or MDS with excess blasts-2 who harbor an IDH1 or IDH2 mutation. IDH1 and IDH2 inhibitors have been also combined with HMA. In a phase 1b/2 study reported by DiNardo, et al. where 17 patients were treated with AZA and either IVOSI (n=11) or ENASI (n=6); ORR reported 72% (8 patients) and 66% (4 cases) with CR rate of 36% (4 cases) and 33% (2 cases), respectively [57]. Similar results was reported by this group in a different phase 1b (NCT02677922) combining IVOSI plus AZA in 23 patients with median age of 76 years (range 61-88); median follow up of 16 months with ORR of 78.3% and CR 60.9% [58].

**Drug-Antibody Conjugates**

Gemtuzumab Ozogamicin (GO) is a humanized recombinant anti-CD33 antibody (huP67.6) conjugated to calicheamicin, an antitumor antibiotic [59]. In AML, Larson, et al. reported the results of three multicenter, open-label, phase 2 studies that evaluated the efficacy and safety of GO monotherapy (9 mg/m² in 2 doses separated by 14 days) in 277 AML patients, including 157 of which were age 60 years or older. The ORR was 26% without a significant difference between young and elderly patients with the median OS of 4.9 months. In those patients who entered remission after receiving >2 doses of GO, the OS was 12.6 months vs. 4.2 months in those who still had evidence of disease [60]. Based on these results, GO was initially approved by the FDA to manage AML patients who were not candidates for IC. Unfortunately, the SWOG S0106 trial results ultimately showed increased in treatment-related mortality related to GO leading to the withdrawal of the medication [61]. Then in the ALFA-0701, a phase 3, open-label, multicenter study, of 280 previously untreated de novo AML with CD33 positivity randomized to standard chemotherapy with or without GO at 3 mg/m² on days 1,4,7,17 patients in GO group without increasing risk of death due to toxicity,17 patients in GO group whom achieved CR/CRp could receive SCT and veno-occlusive disease occurred in 3 of them [62]. In the randomized phase 3 EORTC-GIMEMA AML-19 Trial, GO as single agent was compared to BSC in OA-AML with median age of 77 years (range 62-88) unsuitable for IC; A total of 247 patients were treated with an ORR of 27% with 1 year OS of 24.3% vs. 9.7% in the GO and BSC groups, respectively. no excess in mortality related to toxicities was found in either arms [63]. Moreover, a meta-analysis of five randomized controlled trials of 3325 patients found that GO reduced risk or relapse and improved OS. The authors also found that doses of 3 mg/m² were just as effective as 6 mg/ m² but associated with fewer early deaths [64]. These results led to the re-approval of the medication by the FDA.

**FLT3 Inhibitors**

Fms-like tyrosine kinase 3 (FLT3) is a protein that belongs to the class III family of receptor tyrosine kinase (RTK) that plays a key role in controlling the survival, proliferation, and differentiation of...
hematopoietic cells. FLT3 mutations occur in about a third of elderly with AML, resulting in a constitutively activated FLT3 kinase, leading to proliferation and survival of AML [65,66]. For this reason, FLT3 inhibitors (FLT3i) have an important role in the treatment of AML, as evidenced by the improved OS in the pivotal phase 3 RATIFY trial, which compared the addition of Midostaurin (MIDO) to 7+3 induction vs. chemotherapy alone. Unfortunately, no patients >60 years of age were enrolled in this trial however these data can be considered for elderly fit patients as well [67]. However in a phase II study of adding MIDO to IC followed by consolidation with stem cell transplantation or Hidac and receiving MIDO as maintenance in a mixed age groups (18-70 years old, with 30% more than 60 years old) demonstrated CR/CRi rate of 75.8 Vs.77.9% in age<60 years old and elderly, respectively, 72.4% of patients could go for transplantation followed by MIDO maintenance in 75 patients while the rest (27%) received Hidac consolidation followed by MIDO maintenance. The 2-year EFS and OS were 39% and 34% Vs. 53% and 46% in patients with age<60 years old and older respectively [68]. Gilteritinib, another FLT3i, showed antileukemic activity in combination with AZA in patients ineligible for intensive induction in the first in human phase 1/2 study (CR 67%) [69]. In the randomized phase 3 ADMIRAL trial Gilteritinib was used in R/R AML setting with the median age of patients was 62 years demonstrating significant longer survival and CR/Cri compare to salvage chemotherapy group (9.3 vs. 5.6 months; p<0.001 and 34% vs. 15.3%, respectively [70]. Quasartinib is another selective and highly potent oral FLT3i type II which was investigated in QuANTRUM-R phase 3 randomized trial, although the median age was less than 60 years, it showed longer overall survival (HR 0.76, p 0.02) and median overall survival compare to preselected chemotherapies (LDAC, FLAG-IDA, MEC) group ( 6.2 vs. 4.7 months, respectively) [71]. Sorafenib is another member of this family and was used as a first line treatment (in unfit elderly with untreated FLT3-ITD mutated to receive IC) in combination with AZA (n= 27, age 61-86 years old) demonstrating ORR 78% with CR/Cri rate of 70% and median OS og 8.3 for all group [72].

TP53 Targeted Therapies

The p53 is a tumor suppressor gene that triggers cell cycle arrest, and or apoptosis on cellular stress. TP53 mutation is found in about 10% of OA-AMLAnd in up to 70% of cases with complex karyotype (CK) [18 65]. For many years, no option was available to target this mutation. In 2002, the first compound that could restore sequence-specific DNA-binding, wild-type conformation, and transcriptional transactivation to mutant p53 was reported [73]. Ten years later, Lehmann, et al. described the first-in-human study of Eptenapetop (APR-246), a methylated form of the original compound, in hematologic malignancies [74]. Then, in a phase 1b/2 open-label, multicenter, dose-escalation, and dose-expansion study of treatment naive MDS/AML patients with a median age of 74 years, the combination of AZA and Eptenapetop found an ORR of 64% and CR of 36% in AML patients and a median OS of 10.8 months [75]. Magrolimab (M AGRO) is another medication that has shown activity in TP53 mutated OA-AML. It is a first-in-class antibody targeting CD47, a macrophage immune checkpoint, and a “don’t eat me” signal on cancers. A phase 1b study combining MAGRO/ AZA in AML/MDS patients with a median age of 73 years found an ORR of 69% in AML patients with 50% CR with median survival of 12.9 vs. 18.9 months in TP53- mutant and wild-type, respectively; however subgroup analysis also revealed that 88% of TP53 mutated patients achieved an objective response. [76,77].

Hedgehog pathway inhibitors

Glazdegib is an antagonist of the Hedgehog pathway through binding to Smoothened that can decrease dormant AML leukemic stem cells burden [78]. Based on this information, Cortes, et al. reported a randomized trial comparing LDAC with and without glazdegib in 132 patients with newly diagnosed AML/MDS; more than half of the population was over 75 years of age. After a median follow-up of 21.7 months, median OS in AML group was 8.3 vs 4.4 months in glazdegib vs. LDAC alone arm. Additionally, the ORR was 26.9% vs. 5.3% in the glazdegib and LDAC vs. LDAC alone [78]. Because LDAC is not commonly used in the United States, Shallis, et al. announced a multicenter, randomized phase 2 study evaluating the efficacy of glazdegib combined with two different doses of decitabine in newly diagnosed poor-risk elderly AML patients who either refuse or are ineligible for intensive therapy (NCT04051996). This trial is ongoing.

Immune Checkpoint Inhibitors

Checkpoint inhibitors have become one of the cornerstones in the management of oncologic diseases. Physiologically, they regulate self-tolerance and protect tissue against the potential damage that the immune system can cause by adjusting the signals that mediate T-cell immune response [79]. In AML, there seems to be immune suppression at the level of the bone marrow mediated by overexpression of PD-1 compared to healthy individuals [80]. As with other agents, immune checkpoint inhibitors have been used in the management of relapse/ refractory (R R) AML, but to date, no data have been published, specifically in the elderly as front line. Pembrolizumab in combination with Decitabine currently is under recruiting patients with newly diagnosed/R R AML or myelodysplastic syndrome (MDS) in a phase IB trial (NCT03969446). A phase II study of High dose cytarabine (HiDAC) followed pembrolizumab RR AML enrolled 41% of the population with an age of 60 years or older. The ORR and composite CR (Cri) rates were 46% [29%,63%] and 38% [22%,55%], respectively, meeting the primary endpoint of the study. After a median follow-up of 7.8 months, the median OS was 8.9 months (NCT02768792). In another phase IB/2 study of nivolumab in combination with azacitidine for RR AML; this single-arm trial enrolled patients with a median age of 70 years to receive treatment with both medications. The ORR was 33%, with a CR rate of 22% and a median OS of 6.3 months [81]. In the frontline setting, the combination of pembrolizumab with chemotherapy was evaluated in a phase 2 trial investigating the use of 7+3 and pembrolizumab induction for newly diagnosed AML or MDS. The median age was 54 years, with 20% of patients being over 60 years of age. After a median follow-up of 17.25 months, 55% of patients were alive (with a median of 18.5 months) with ORR (CRI+CRI+CRp) of 78% (34/44) [82]. Unfortunately, the outcomes of the elderly patients were not described separately. Therefore, further data is needed to define the role of these medications in the management of AML in OA-AML.

Bispecific T-cell engagers (BiTE)

Bispecific T-cell engagers are antibody constructs that link T cells to tumor antigens, leading to activation of cytotoxic response [83]. Several BiTEs are currently being evaluated for AML; Flotetzumab is a CD123/ CD3 BiTE studied in a phase 1/2 study of 122 patients (median age of >60 years) with primary induction failure (PIF), early relapse (ER), or RR AML. The ORR for RR and PIF/ER was 24% and 30%, respectively. The study also reported 6- and 12-month survival rates of 42% (0.237, 0.596) and 20% (0.025, 0.377) for PIF/ER (n = 30), respectively. Most patients experienced some degree of cytokine release syndrome (CRS),
but most of them (81%) had mild to moderate symptoms. Neurologic involvement was infrequent, seen in only 10% of cases [84]. AMG 330 is a BiTE that binds to CD33 and CD3. In a phase 1, open-label dose-escalation study, 55 patients with a median age of 58 years, including individuals up to 80 years of age, reported an ORR of 19%. No survival data have been reported, and this study is still ongoing [85]. Other BiTEs, such as AMG637, AMG 427, AMV564, and XmAb14045, are currently under study. While some responses have also been seen, they are modest at best in early phase trials [86-88].

Chimeric Antigen Receptor T-Cell Therapy (CAR-T)

Currently, ACT is administered as genetically engineered Chimeric Antigen Receptor (CAR) T cells [89]. This treatment modality has successfully treated refractory hematologic malignancies (ALL, Lymphomas, multiple myeloma), as evidenced by high remission rates in this high-risk patient population [90-93]. AML, as previously mentioned, is a heterogeneous disease, and therefore finding an optimal target has been challenging. To date, different CAR-Ts have been used in the setting of in-vivo AML with promising findings [94-99] and currently several AML CAR-T trials targeting different antigens like CD33 (NCT03971799), CD38 (NCT04351022), CD123 (NCT03190278), and NKGD2 (NCT02203825), are underway mainly in the relapse/refractory setting, though not specifically for the elderly population.

Allogeneic Hematopoietic Stem Cell Transplantation

Despite all the advances AML still is associated with poor outcomes in the elderly however, in a large multicenter retrospective study (alliance A151509, SWOG, ECOG-ACRIN, and CIBMTR) comparing outcomes of patients consolidated with allo-HSCT vs. more chemotherapy indicating allo-HSCT had more Treatment-Related Mortality (TRM) in the first 9 months (p = 0.0009) but with significantly reduced relapse rate beyond 9 months (p < 0.0001) and superior long term OS at 5 years (29% vs. 13.8%) [100,101]. The role of myeloablative conditioning regimen (MAC) in elderly is not robust mainly because of more co-morbidities in patients and TRM in MAC compare to Reduced intensity regimen (RIC). The CALGB 100103 phase 2 study more prospectively assessed the efficacy of RIC in patients (age of 60 to 74 years) with AML in CR1. The study authors found a 2-year OS of 42% with disease free survival (DFS) of 50%, NRM 15%, and Cumulative Incidence of Relapse (CIR) of 44% [102]. A meta-analysis of 13 studies reported an OS of 38% at 3 years with a corresponding relapse-free survival (RFS) of 35% and NRM of 40% [103]. More recently, Del Galy, et al. reported their real-world experience in OA-AML treated with IC or HMA followed by reduced-intensity conditioning (RIC) allo-HSCT. Of the entire cohort, the transplantation rate was 35% in those achieving CR with a median age of 68 years. With a median follow-up of 44 months, the estimated OS was 50 months in patients who underwent transplant vs. 20.6 months in no-transplant group. Additionally TRM was <5%, with 2 years relapse rate of 45% contributing using RIC instead of MAC in a group of elderly patients with median HCT-Cl of 3 [104]. While myeloablative conditioning (MAC) regimens have also been used with a reported 3 years OS, NRM, and relapse rate of 34%, 43%, and 24%, respectively [105]. For these reasons, RIC allo-HSCT is considered the most effective therapy to obtain durable remissions in OA-AML. This benefit is believed to be related to its graft vs. leukemia (GVL) effect in addition to better supportive care [106]. Unfortunately, about <10% of OA-AML get transplanted despite of the clear benefit in survival.

Conclusions

In conclusion, OA-AML is a population at increased risk for poor outcomes related not only to underlining hematological malignancies but also to underlying physiologic deterioration related to age. In the management of this patient population multiple factors should be taken into consideration (performance status, disease status, gene mutation profile, etc.) before choosing the treatment. While new therapies have proven to be effective in the management of OA-AML, long term follow up is needed to determine the impact on outcomes. Lastly, if the individual can tolerate, RIC allo HSCT should be offered to these patients as is the single most important treatment that has been repeatedly shown to improve long-term disease-free survival (DFS) in this population.

Conflict of Interest disclosure

GM: speakers’ bureau for AbbVie and Novartis, advisory board with Janssen, MAL: advisory board with Gilead. The rest of the authors with no conflict of interest.

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