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Review

Trials and Tribulations in the Frontline Treatment of Older Adults with Acute Myeloid Leukemia

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Abstract: Acute myeloid leukemia (AML) is a heterogeneous aggressive hematologic malignancy derived from malignant clones that promote their own growth and survival at the expense of normal hematopoiesis resulting in life-threatening bleeding and infections. Traditional initial AML therapy has been centered on a backbone of intensive chemotherapy often composed of an anthracycline and cytarabine. This strategy has proven most effective in patients less than 60 years of age due to both patient-related tolerability factors as well as changes in AML biology centered on chemotherapy refractory mutational profiles that are seen with advancing age. Recent improvements in frontline AML therapy have been seen in patients 60 years of age and over, a population most typically referred to as "older" adult AML. Herein, we describe the characteristics of "older" adult AML, review the differences in outcomes amongst those 60–75 and those over 75 years of age, and cite challenges in delivering frontline therapies within this group based not only on therapeutic toxicity but also on the patient's overall level of "fitness" and inherent biology. We also discuss the role of targeted therapies that inhibit specific mutations and have the potential to deliver improved efficacy with less side effects while also recognizing that some selected older AML patients still benefit from intensive induction therapy.

Keywords: acute myeloid leukemia; older adult; frontline treatment

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1. Introduction

Acute myeloid leukemia (AML) is an aggressive hematologic malignancy affecting about 0.5% of people in their lifetime. Over the last few decades, a growing understanding of AML has revealed it to be a heterogenous disease with a widely variable prognosis. This is largely driven by disease biology, the ability to tolerate highly toxic multi-agent chemotherapy and, in most cases, undergo allogeneic stem cell transplantation to be cured of disease. In the best of circumstances, this is a tenuous situation with life-altering implications. Our review will focus on the characteristics of AML in "older" patients and discuss frontline management approaches for this population that can range in terms of performance status from "fit" to medically "frail". We also discuss future directions for treatment in this disproportionately afflicted, vulnerable population.

2. AML in "Older" Adults

While induction chemotherapy with a combination of an anthracycline and anti-metabolite has served as the backbone for the curative treatment of AML, this is highly toxic and may not be feasible to give to all patients. Furthermore, with the median age at AML diagnosis of 68 years old and the highest rates of AML in individuals in their eighth and ninth decades of life, there are often several competing factors altering prognosis and treatment compared with their younger counterparts. These include both patient and disease factors. The definition of "older" varies by study and guidelines [1,2]. For the purposes of this review, we will focus on the treatment of patients age 60 and older with non-promyelocytic acute myeloid leukemia.

2.1. Biology of Disease

AML is a highly heterogeneous disease, with a range of understanding regarding the molecular and cytogenetic factors affecting prognosis and treatment. Older patients have numerous features that contribute to worse outcomes compared with in younger patients. High rates of primitive (CD34+) leukemic blasts, antecedent hematologic disorders, and trilineage dysplasia are present [3,4]. Furthermore, high rates of multidrug resistance-1 (MDR-1) expression leading to increased potential for chemotherapy extrusion are common [3,4].

In the SWOG-9031 trial, 71% of the elderly patients (age 55 and older) expressed MDR-1, and 25% of patients had adverse cytogenetics, while only 4% had favorable cytogenetics [5]. Suarez et al. later found higher expression of the multidrug resistance (MDR) protein, P-gp, and lower expression of the anti-apoptotic protein, APO2.7, in CD34+ leukemic blasts amongst elderly patients. However, the expression of P-gp was not statistically different between younger and older patients with CD34+ blasts [4]. These findings raise concern regarding the inherent resistance of leukemic stem cells to cytotoxic chemotherapy, rendering intensive treatment approaches less effective.

In older adults, monosomal karyotypes, -5 and -7, as well as other adverse cytogenetic abnormalities, including 17p, 11q, +8, and complex karyotypes predominate, while favorable cytogenetic abnormalities are uncommon [3]. In a cytogenetic analysis of CALGB-8461 that compromised patients over 60 years with predominantly de novo AML (97.5%), a complex karyotype with $\geq$3 abnormalities (19% of patients) and "rare aberrations" (5% of patients) were associated with lower complete remission (CR) rates, while complex karyotype with $\geq$5 abnormalities (15% of patients) and "rare aberrations" were also associated with inferior disease-free survival (DFS) and overall survival (OS) [6].

Another cytogenetic analysis of AML patients over 60 years old treated with induction chemotherapy in the HD98-B protocol showed adverse cytogenetics present in 35% of enrolled patients and once again was associated with an inferior OS (HR 2.24; 95% CI: 1.74–2.88). Favorable cytogenetics were associated with a median OS of 26.4 months compared with just 5.1 months for patients with adverse disease. Patients over the age of 70 years old with adverse cytogenetic features fared even more dismally, with a median OS of 3.1 months compared to 6.3 months for those over 70 years old without adverse features [7]. A more recent German study of patients age 75 years or older treated intensively for AML found *TET2* (42%), *DMNT3A* (35%), *NPM1* (32%), *SRSF2* (25%), and *ASXL1* (21%) to be the most common mutations and, once more, corroborated that adverse cytogenetics by the UK Medical Research Council (MRC) classification were associated with poorer OS.

Furthermore, *IDH1* mutations had poor complete response (CR) rates and survival [8], which has been corroborated by additional studies even when *NPM1* is present [9]. When examined in and of themselves, *NPM1* mutations appear to still confer a favorable prognosis in older adults treated with intensive chemotherapy [10,11] although the data re conflicting [12]. Genetic risk classification based on European LeukemiaNet remains the most widely used risk stratification system for both "young" and "older" adults with AML. Notably, patients with *ASXL1* and *p53* mutations, which are prevalent in older adults, are at adverse risk while *NPM1* mutations without a high allelic ration *FLT-ITD* mutation are favorable [13].

2.1.1. Secondary AML

Antecedent hematologic disorders, like myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPNs), can eventually lead to secondary AML (sAML). MDS and MPNs are cancers that are secondary to clonal aberrations in myeloid development, while sAML usually develops through clonal evolution with a different subclone emerging during the disease course that is apart from the initial dominant clone. The majority of sAML (60% of cases) evolves from MDS with the remainder evolving from MPNs, including chronic myelomonocytic leukemia. Secondary AML in total accounts for 20–25% of all AML cases and, as with de novo AML, has a median age of onset in the mid 60s, thereby,

underscoring its preponderance in the older adult population [14,15]. The importance and characteristic findings of sAML are exemplified by the 2016 designation by the World Health Organization of AML developing from MDS as a distinct clinicopathologic entity termed "AML with myelodysplasia-related changes" (AML-MRC) [16].

Historically, a sAML diagnosis has been based solely on the blast count. Those patients with less than 20% blasts are given a diagnosis of MDS, while those patients with 20% or more blasts are said to have "transformed" to AML. This paradigm has been challenged as of late by evidence for specific genetic mutations present in the founding clone and subsequent daughter subclones in the progression of MDS to sAML that represent defined patterns that could identify progression to AML before the 20% myeloblast threshold is reached [17].

Furthermore, while there is a difference in the types of mutations and mutational variant allele frequencies (VAFs) between MDS and AML, this difference is no longer apparent when high-risk MDS is compared to AML, thereby, suggesting that high-risk MDS and AML represent a continuum of the same disease with the same response to therapy and similar prognoses [18]. Clonal evolution with the acquisition of additional mutations is also a hallmark of AML derived from MPNs and, like sAML from MDS, carries a poor prognosis [19].

The clonal evolution of sAML from an antecedent MDS often leads to a monosomal or complex karyotype while *TP53*, *ASXL1*, *TET2*, *DNMT3A*, *IDH1/2*, and *NRAS/KRAS* mutations are often seen in sAML with both prior MDS and MPNs [19,20]. Most importantly, those patients with sAML and antecedent MDS often have already been exposed to and progressed through hypomethylator therapy.

2.1.2. Age

Age in and of itself is a critical factor in the prognosis and treatment selection in AML. Diminished complete response rates and overall survival have been a hallmark of AML studies. The initial CALG studies that identified 7 + 3 as the standard therapy for AML show a clear distinction the in the complete remission (CR) rates and increased risk of death with induction between those <60 and those 60 and older [21,22]. Worsening outcomes with advancing age has been seen in subsequent decades as well with CR rates in the 70–80% range for patients <40-years-old, 60–70% for 40–60-years-old; and 50–60% in those >60 [23–26].

A critical division regarding outcomes is even seen amongst the age 60 and over patient subgroup. The HD98-B trial included 361 patients over 60 years old treated with intensive chemotherapy and found that age over 70 was independently associated with inferior OS (HR 2.34; 95% CI: 1.77–3.08) [7]. When further stratified by the presence of adverse cytogenetics, survival was best amongst patients under 70 years old without adverse changes (3-year OS: 26%, median OS 17.5 mos) followed by patients under 70 years old with adverse features OR over 70 years old without adverse changes (3-year OS: 6%; mOS 7.2 mos and 6.3 mos, respectively) and lastly patients over 70 years old with adverse cytogenetics (3-year OS: 2%; mOS 3.1 mos) [7].

Despite these patients being able to tolerate intensive chemotherapy, most patients did not fare well given their age and/or cytogenetic features [7]. Interestingly, in regards to non-trial data, an analysis of the SEER database found improvements in the response rates (RR) and 12-month survival with each decade from 1977–2006 for patients who were 65–74 years old but no improvement for their 75 years of age and older counterparts despite the approval of agents to treat older patients within this timeframe [27]. This variation in survival underscores a need to discuss the prognosis and treatment of those between age 60 and 74 years old and patients 75 years old or more separately. Later in this review, we discuss the treatment of those between age 60 and 74 years old and patients 75 years old or more separately.

2.2. Comorbidities

In addition to biological age, concomitant health conditions and their treatments may limit chemotherapeutic options and/or require dose reductions. One retrospective study found that patients over 60 years old had higher rates of diabetes and higher baseline Charleston Comorbidity indexes (CCI) than those younger than 60 years [24]. Additionally, higher mean blood glucose levels and greater blood glucose variability are associated with significantly lower remission rates and higher mortality rates in older patients [24]. Polypharmacy is another important aspect to keep in mind when caring for older AML patients. The use of four (4) or more medications is associated with lower CR rates, increased 30-day mortality, and overall mortality than one medication or less [28].

A tool to consider when assessing a patient's ability to tolerate induction chemotherapy is the hematopoietic cell transplant comorbidity index (HCT-CI). The HCT-CI was initially created to assess the risk of non-relapse mortality and survival before allogeneic stem cell transplantation. Hence, it is a risk score that incorporates a number of significant comorbidities. HCT-CI was also found to be predictive of overall survival and early death rates in elderly (60 years and older) AML patients with induction therapy [29].

2.3. Geriatric Assessment

Standardized performance status assessments, such as the Eastern Cooperative Oncology Group (ECOG) performance status or Karnofsky performance status (KPS), are the backbone of assessing a patient's ability to receive treatment. These assessments serve as the benchmark for assessing fitness for clinical trial enrollment. However, they are limited and can miss significant frailty and disability in the heterogenous and vulnerable elderly population. Comprehensive geriatric assessments (GA) evaluate comorbidities, nutritional status, polypharmacy, functional status, cognitive function, and test for geriatric syndromes (frailty, depression, anxiety, etc.).

While not initially created for the assessment of oncology patients, they have subsequently been found to predict mortality and chemotherapy-related adverse effects [30,31]. AML and its treatment is among the most intensive stressors that a person can experience. Often, it evolves rapidly and may even require lengthy hospitalization and intensive supportive care. Several studies have gone on to assess the role and feasibility of geriatric assessments in patients receiving induction chemotherapy and even stem cell transplantation for AML in order to accurately depict the effect of induction chemotherapy on older patients [32–38].

Klepin et al. initially reported the feasibility of a bedside geriatric assessment and noted its ability to uncover impairments beyond those captured by subjective performance status [32]. Impairments in cognition and objectively measured physical function, assessed by GA were associated with worse overall survival in older patients receiving induction chemotherapy for AML [33]. Furthermore, older patients with FLT3-mutated AML on clinical trial were found to have a decline in several domains of their GA, including their physical function, nutritional parameters, social activity, and mental health [36]. A decline in objective physical function and depression were also associated with worse OS during post-remission therapies [37].

In patients treated with "non-intensive" regimens, KPS < 80, an elevated fatigue index, and a diminished activity of daily living (ADL) index were associated with worse overall survival, which was seen in patients treated with best supportive care only or hypomethylating agents [35]. Utilizing the information obtained from GAs and combining it with cytogenetic and molecular information to optimally tailor individual treatment within this heterogenous group is under study and likely represents a step forward in the treatment of AML in older adults [39].

3. Initial Treatment

AML is an aggressive, rapidly progressive, and fatal disease if left untreated. However, it can be responsive to curative and palliative chemotherapy treatments. While a variety of

treatments have been studied, the first decision point remains an assessment of the patient's fitness. Historically, combination induction chemotherapy was the best option for attaining remission. However, as additional agents and combinations are studied, we have found that other "less" intensive options may also lead to remission. After an assessment of the patient fitness, treatment may be further guided by the cytogenetic and molecular variables specific to each person's disease [1]. Below, we discuss some of the frontline treatment options available. Careful assessment of the patient, their level of fitness, biologic aspects of their leukemia, and their social support structures is needed prior to therapy selection.

3.1. "Fit" Induction Therapy

The standard treatment approach for patients who are deemed "fit" for intensive treatment remains a backbone of an anthracycline and cytarabine ('7+3') in a variety of formulations and dosages and in combination with other drugs. The ideal dose and choice of anthracycline is not entirely clear. A phase 3 study by ECOG (Table 1) showed no difference in the response rates or survival between daunorubicin 45 mg/m^2 on days 1–3, mitoxantrone 12 mg/m^2 on days 1–3 or idarubicin 12 mg/m^2 on days 1–3 when combined with cytarabine 100 mg/m^2 continuous on days 1–7 [40]. Another phase 3 study by Ohtake et al. comparing daunorubicin 50 mg/m^2 with idarubicin 12 mg/m^2, showed similar outcomes [41].

Lowenberg et al. reported on a phase 3 study of patients age 60 years and older who were randomized to daunorubicin 45 mg/m^2 on days 1–3 or daunorubicin 90 mg/m^2 on days 1–3 [25]. Both groups received this with a seven-day continuous infusion of cytarabine 200 mg/m^2 and later received cytarabine 1000 mg/m^2 every 12 h for 6 days following their induction cycle [25]. The overall cohort had significantly higher CR rates after both the first cycle (52% vs. 35%, $p < 0.001$) and second cycle (64% vs. 54%, $p = 0.002$) without higher rates of hematologic toxicities, 30-day mortality, or moderate-life threatening adverse effects [25].

This failed to result in an improvement in the event-free survival (EFS) or OS. However, in patients between 60–65 years old, escalated-dose daunorubicin resulted in higher CR rates (73% vs. 51%, 0.02), EFS (29% vs. 14%, $p = 0.02$), and OS (38% vs. 23%, $p = 0.007$) compared to standard-dose daunorubicin [25]. Additionally, there was no difference in CR or EFS between these two dose levels in core-binding factor (CBF) leukemias.

Table 1. Intensive induction regimens for AML with an emphasis on older adult outcomes.

Study/Author	Phase/Population	Median Age (Years) [Range]	Study Medication	CR	DFS/EFS/PFS/RFS	OS
Anthracycline + Cytarabine-Based Regimens						
ECOG E3993; Rowe et al. [40]	III, 348 patients (≥55 years old) with newly diagnosed AML fit to receive 7 + 3 induction chemotherapy	**Daunorubicin** 67 (56–82) **Mitoxantrone** 69 (56–84) **Idarubicin** 67.5 (56–86)	**Daunorubicin** 45 mg/m^2 vs. **Mitoxantrone** 12 mg/m^2 vs. **Idarubicin** 12 mg/m^2. **All** on days 1–3 All received cytarabine 100 mg/m^2 cont. on days 1–7.	**All**: CR 42% **Daunorubicin** CR 40% **Mitoxantrone** CR 46% **Idarubicin** CR 43%	**All**: Median DFS 7 mo **Daunorubicin** Median DFS 5.7 mo **Mitoxantrone** Median DFS 7.1 mo **Idarubicin** Median DFS 9.4 mo	**All**: mOS 7.5 mo **Daunorubicin** mOS 7.7 mo **Mitoxantrone** mOS 7.5 mo **Idarubicin** mOS 7.2 mo
JALSG AML201; Ohtake et al. [41]	III, 1057 patients (age 15–64 years old) with de novo AML fit to receive 7 + 3 induction chemotherapy	**All**: 47 (15–64) **Daunorubicin** 47 (15–64) **Idarubicin** 47 (15–64)	**Daunorubicin** 50 mg/m^2 days 1–5 vs. **Idarubicin** 12 mg/m^2 days 1–3. **All** received cytarabine 100 mg/m^2 cont. on days 1–7.	**All**: CR 77.9% **Daunorubicin** CR 77.5% **Idarubicin** CR 78.2%	**Daunorubicin** 5-yr predicted RFS 41% **Idarubicin**5-yr predicted RFS 41%	**Daunorubicin**5-yr predicted OS 48% **Idarubicin** 5-yr predicted OS 48%
HOVON-43-AMLSAKK 30/01; Lowenberg et al. [25]	III, 813 patients (≥60 years old) with newly diagnosed AML or RAEB with IPS of 1.5 or greater fit to receive 7+3 induction chemotherapy	67 (60–84) 26% > 70 years	**Daunorubicin** 45 mg/m^2 vs. 90 mg/m^2 on days 1–3. All received cytarabine 200 mg/m^2 cont. on days 1–7.	**1st cycle CR** 35% vs. 52% ($p < 0.001$) **After consolidation CR** 54% vs. 64% OR 1.59 [1.18–2.15] ($p = 0.002$) **60–65 yr old** CR51% vs. 73% OR 2.64 [1.63–4.29]($p = 0.02$)	**All EFS** 17% vs. 20% ($p = 0.12$) **60–65 yr old EFS** 14% vs. 29% OR 0.68 [0.53–0.87] ($p = 0.02$) **All DFS** 29% vs. 30% ($p = 0.77$) **60–65 yr old** DFS 27% vs. 39% ($p = 0.43$)	**All OS** 26% vs. 31% ($p = 0.16$) **60–65 yr old** OS 23% vs. 38% OR 0.65 [0.50-0.84] ($p = 0.007$)
NCRI-AML17; Burnett et al. [42]	III, 1206 patients (≥16 years old) with newly diagnosed AML or high-risk MDS (>10% blasts) fit to receive 7 + 3 induction chemotherapy	53 (16–72) 26% ≥ 60 years	**Daunorubicin**: 60 mg/m^2 vs. 90 mg/m^2 on days 1–3. All patients received cytarabine 100 mg/m^2 q12h on days 1–10. All patients received a second induction containing daunorubicin 50 mg/m^2 except subset of adverse-risk pts who received FLAG-IDA.	**CR + CRi** 82% 84% vs. 81% ($p = 0.2$) **1st cycle CR + CRi** 66% vs. 68% ($p = 0.4$) **CR** 75% vs. 73% ($p = 0.6$)	**2-yr RFS** 48% vs. 51% ($p = 0.7$)	**2-yr OS** 60% vs. 59% ($p = 0.15$)
NCT01145846;Lee et al. [43]	III, 209 patients (15–65 years old) with newly diagnosed AML fit to receive 7 + 3 induction chemotherapy	**Overall** 49 (15–65) **Daunorubicin** 48.5 (15–65) **Idarubicin** 49 (15–65)	**Daunorubicin** 90 mg/m2 vs. **Idarubicin** 12 mg/m2All on days 1–3. All received cytarabine 200 mg/m^2 cont. on days 1–7.	**OverallCR** **Total** 77.6% 74.7% vs. 80.5% ($p = 0.224$) **CR after 1 induction course** **Total** 69.2% 66.7% vs. 71.1% ($p = 0.403$)	**4-yr EFS** 48.2% 50.8% vs. 45.5% ($p = 0.772$)	**4-yr OS** 52.8% 54.7% vs. 51.1% ($p = 0.756$)

Table 1. *Cont.*

Study/Author	Phase/Population	Median Age (Years) [Range]	Study Medication	CR	DFS/EFS/PFS/RFS	OS
ALFA-9801; Pautas et al. [44]	III, 468 adult patients (50–70 years old) with newly diagnosed AML (no prior MPN or MDS) fit to receive 7 + 3 induction chemotherapy	**Overall** 60 (NR) **Idarubicin** 3d 59.8 (NR) **Idarubicin** 4d 60 (NR) **Daunorubicin** 59.7 (NR)	**Idarubicin** 12 mg/m^2 on days 1–3 vs. 12 mg/m^2 on days 1–4 vs. **Daunorubicin** 80 mg/m^2 on days 1–3. **All** received cytarabine 200 mg/m^2 cont. on days 1–7.	**CR** **All** 77% 83% vs. 78% vs. 70% OR 1.75 (p = 0.04) p = 0.007 for Idarubicin 3d vs. Daunorubicin	**2-yr EFS** 23.5% **4-yr EFS** 18% EFS did not differ between 3 arms (p = 0.19)	**Median OS** 17 mo **2-yr OS** 38% **4-yr OS** 26.5% OS did not differ between 3 arms (p = 0.19)
ALFA-0701; Castaigne et al. [45]	III, 278 adult patients (50–70 years old) with de novo AML fit to receive 7 + 3 induction chemotherapy	62.2 (58.5–66.3) **Gemtuzumab** 62.8 (59.3–66.8) **Control** 61.7 (57.4–65.6)	**Gemtuzumab ozogamicin** 3 mg/m^2 [max 5 mg] days 1, 4, 7 for study arm. All received daunorubicin 60 mg/m^2 on days 1–3 and cytarabine 200 mg/m^2 cont. on days 1–7.	**CR + CRp** 81% vs. 75% (p = 0.25) **CR** 73% vs. 72%	**2-yr EFS** 40.8% vs. 17.1% HR 0.58 [0.43–0.78] (p = 0.0003) **2-yr RFS** 50.3% vs. 22.7% HR 0.52 [0.36–0.75] (p = 0.0003)	**2-yr OS** 53.2% vs. 41.9% HR 0.69 [0.49–0.98] (p = 0.0368)
Hills et al. [46]	Meta-analysis, 3325 patients (≥15 years old) with newly diagnosed AML or high-risk MDS who were enrolled in randomized clinical trials	58 (15–84)	Gemtuzumab ozogamicin (varying dose schedules) + induction chemotherapy vs. induction chemotherapy alone.	**CR + CRp** OR 0.91 [0.77–1.07] (p = 0.3)	**RFS** OR 0.84 [0.76–0.92] (p = 0.0003)	**OS** **Median (All)**: 22.5 mo OR 0.85 [0.77–0.94] (p = 0.002) **Fav Cyto** OR 0.47 [0.31–0.74] (p = 0.0006) **Intermed Cyto** OR 0.84 [0.75–0.95] (p = 0.005)
ALFA-0701; Lambert et al. [47]	III, 271 adult patients (50–70 years old) with de novo AML fit to receive 7 + 3 induction chemotherapy in modified ITT analysis	62 (50–70) **Gemtuzumab** 62 (50–70) **Control** 61 (50–70)	Same as above.	CR + CRp 81.5% vs. 74.1% (p = 0.15) CR 70.4% vs. 69.9%	Median **EFS** 17.3 mo vs. 9.5 mo HR 0.56 [0.42–0.76] (p = 0.0002) **Median RFS** 28.0 mo vs. 11.4 mo HR 0.53 [0.36–0.76] (p = 0.0006)	**Median OS** 27.5 mo vs. 21.8 mo HR 0.81 [0.60–1.09] (p = 0.16)
RATIFY; Stone et al. [48]	III, 717 adult patients (age 18–59 years old) with newly diagnosed, *FLT3*-mutated AML fit to receive 7 + 3 induction chemotherapy	47.9 (18–60.9) **Midostaurin** 47.1 (19–59.8) **Placebo** 48.6 (18–60.9)	**Midostaurin** 50 mg PO BID vs. placebo PO BID on days 8–21 of induction and consolidation cycles. All patients received daunorubicin 60 mg/m^2 on days 1–3 and cytarabine 200 mg/m^2 on days 1–7.	**CR** 59% vs. 54% (p = 0.15)	**Median EFS** 8.2 mo vs. 3.0 mo HR 0.78 [0.66–0.93] (p = 0.002) **4-yr EFS** 28.2% vs. 20.6% **Median DFS** 26.7 mo vs. 15.5 mo (p = 0.01)	**Median OS** 74.7 mo vs. 25.6 mo HR 0.78 [0.63–0.96] (p = 0.009) **4-yr OS** 51.4% vs. 44.3%

Table 1. *Cont.*

Study/Author	Phase/Population	Median Age (Years) [Range]	Study Medication	CR	DFS/EFS/PFS/RFS	OS
NCT00788892; Lancet et al. [49]	II, adult patients (60–75 years old) with newly diagnosed AML fit to receive 7 + 3 induction chemotherapy	**CPX-351**: 68 (60–77) 7 + 3: 68 (61–77)	**CPX-351** on days 1, 3, 5 of initial induction vs daunorubicin 60 mg/m^2 on days 1–3 and cytarabine 100 mg/m^2 on days 1–7 of induction cycle. Consolidation cycles with CPX-351 or 5 + 2 or IDAC.	**CR + CRi** **All** 66.7% vs. 51.2% **sAML** 57.9% vs. 31.6% **CR** **All** 48.8% vs. 48.8% **sAML** 36.7% vs. 31.6%	**Median EFS** **All** 6.5 mo vs. 2.0 mo (p = 0.36) **sAML** 4.5 mo vs. 1.3 mo HR 0.59 (p = 0.08)	**Median OS** **All** 14.7 mo vs. 12.9 mo (p = 0.61) **sAML** 12.1 mo vs. 6.1 mo HR 0.46 (p = 0.01)
NCT01696084; Lancet et al. [50]	III, 309 adult patients (60–75 years old) with newly diagnosed "high-risk"/sAML fit to receive 7 + 3 induction chemotherapy	**CPX-351** 67.8 (NR) 7 + 3 67.7 (NR)	Same as above.	**CR + CRi** 47.7% vs. 33.3% (p = 0.016) **CR** 37.3% vs. 25.6% (p = 0.04)	**Median EFS** 2.53 mo vs. 1.31 mo HR 0.74 [0.58–0.96] (p = 0.021)	**Median OS** 9.56 mo vs. 5.95 mo HR 0.69 [0.52–0.90] (p = 0.003) **1-yr OS** 41.5% vs. 27.6% **2-yr OS** 31.1% vs. 12.3%
Benitez et al. [51]	Retrospective, 169 adult patients (≥18 years old) with newly diagnosed sAML	**CPX-351** 67 (31–80) **HIDAC-based** 67 (27–82)	CPX-351 vs. regimens with purine analog and HIDAC.	**CR + CRi** 47.9% vs. 62.7% (p = 0.002 for non-inferiority) **CR** 41.5% vs. 49.3% (p = 0.352)	**Median EFS** 4.11 mo vs. 5.56 mo (p = 0.48)	**Median OS** 9.1 mo vs. 9.8 mo (p = 0.88) **30-day mortality** 8.5% vs. 1.3% (p = 0.039)
FOSSIL; Vulaj et al. [52]	Retrospective, 106 adult patients (>18 years old) with treatment-naïve sAML	**FLAG** 63 (27–82) 7+3 60 (21–76)	FLAG vs. 7 + 3.	**CR + CRi** 65% vs. 45% (p = 0.071) **ORR (CR + CRi + MLFS)** 70% vs. 48% (p = 0.043)	**Median RFS** 4 mo vs. 5 mo (p = 0.101)	**Median OS** 8.5 mo vs. 9.1 mo (p = 0.798)
NCT03214562; Lachowiez et al. [53]	Ib/II, cohort of 24 adult patients (>18 years old) with newly diagnosed AML	44	FLAG-IDA + Venetoclax.	**CR + CRi + CRh** 89%	**Median EFS** Not reached	**Median OS** Not reached **1-yr OS** 92%

In contrast, the phase 3 NCRI-AML17 study showed no difference in the CR rates or 2-year OS between daunorubicin 60 mg/m^2 and 90 mg/m^2 induction regimens, but higher-dose daunorubicin did result in a higher 60-day mortality (10% vs. 5%, $p = 0.001$) [42]. This study was conducted in largely younger patients, utilized a lower dose of cytarabine (100 mg/m^2 continuous for seven days), and most notably was followed by a second daunorubicin-containing induction course [42]. While this may suggest that 90 mg/m^2 is not superior to 60 mg/m^2, the second induction also raises the question if there is a dose threshold for the optimal effect.

A phase 3 study comparing idarubicin 12 mg/m^2 on days 1–3 to daunorubicin 90 mg/m^2 on days 1–3 in patients age 15–65 years old showed no differences in the CR rates, relapse, or survival [43]. However, a higher EFS and OS were seen in patients with FMS-like tyrosine kinase 3-internal tandem duplication (FLT3-ITD) mutations who received daunorubicin compared with idarubicin [43]. ALFA-9801 found no difference in EFS, relapse rates, or OS between daunorubicin 80 mg/m^2 on days 1–3, idarubicin 12 mg/m^2 on days 1–4 or idarubicin 12 mg/m^2 on days 1–3 in patients between 50–70 years old. Notably, both idarubicin arms resulted in higher CR rates than daunorubicin [44].

The addition of gemtuzumab ozogamicin (GO), an antibody-drug conjugate that binds to CD33, presents another alternative to induction therapy in older patients. The ALFA-0701 study evaluated the impact of the addition of GO 3 mg/m^2 (max 5 mg) on days 1, 4, and 7 to a backbone of daunorubicin 60 mg/m^2 on days 1–3 and cytarabine 200 mg/m^2 continuous on days 1–7 followed by two consolidation courses composed of daunorubicin and cytarabine with or without GO [45].

During the initial analysis, the addition of GO resulted in a significantly better 2-year EFS (40.8% vs. 17.1%, 0.0003), 2-year OS (53.2% vs. 41.9%, $p = 0.0368$), and 2-year relapse-free survival (RFS) (50.3% vs. 22.7%, $p = 0.0003$) compared with the chemotherapy backbone alone, without worse treatment-related mortality (TRM) [45]. In subgroup analyses, patients with favorable and intermediate risk cytogenetics appeared to preferentially benefit from the addition of GO [45]. A subsequent meta-analysis also confirmed improvement in both RFS and OS in patients without adverse cytogenetics [46]. However, this meta-analysis was performed prior to the final analysis of ALFA-0701, which reported that the significant OS benefit did not persist [47].

For patients with FLT3-ITD, the standard of care is based upon the results of the phase 3 RATIFY trial comparing daunorubicin 60 mg/m^2 on days 1–3 and cytarabine 200 mg/m^2 continuously on days 1–7 with and without midostaurin 50 mg by mouth twice daily on days 8–21 of induction. Additional consolidation courses with and without midostaurin were also a part of the protocol [48]. This resulted in improved EFS and OS. This study, however, was potentially limited by a control arm in which daunorubicin was only dosed at 60 mg/m^2, which in patients 65 years and younger could be considered non-standard of care [48].

Lastly, are the intensive treatment options for secondary AML (sAML) including therapy-related AML, antecedent MDS/CMML, and AML with myelodysplastic related changes. The current standard of care for sAML patients 60 years and older is CPX-351, or liposomal formulation of cytarabine and daunorubicin in a 5:1 fixed molar ratio. The phase 2 study initially reported improved response rates (57.6% vs. 31.6%, $p = 0.06$ with pre-defined one-sided p-value for significance of $p < 0.1$) without significantly worse TRM, and no improvement in EFS or OS [49] compared to '7 + 3' arm (daunorubicin 60 mg/m^2 and cytarabine 100 mg/m^2).

The authors did not provide extensive reasoning for their p-value selection, only noting that a less stringent p-value was selected to provide a basis for phase 3 study design, rather than replace it altogether. The subsequent phase 3 study, in contrast, did show improvement response rates (47.7% vs. 33.3%, $p = 0.016$), median EFS (2.53 months vs. 1.31 months, $p = 0.021$) and median OS (9.56 months vs. 5.95 months, $p = 0.003$) [50]. The OS benefit was seen amongst all age subgroups. The CPX-351 arm also experienced prolonged time to neutrophil and platelet recovery, and the study had some additional issues, including sub-optimal control arm selection that have raised concern about its generalizability [51].

CPX-351 is now being studied in combination with the BCL-2 inhibitor, venetoclax in frontline and relapsed settings [54].

A retrospective study comparing the outcomes of high-dose cytarabine (HIDAC) based regimens and CPX-351 found no difference in the CR/CRi (complete remission with incomplete count recovery) or median OS between HIDAC and CPX-351, with a lower 30-day mortality for patients receiving HIDAC (1.3% vs. 8.5%, $p = 0.039$) [51]. The FOSSIL study compared FLAG (fludarabine, high-dose cytarabine and g-CSF) with '7 + 3' in sAML [52].

FLAG resulted in a higher ORR (70% vs. 48%, $p = 0.043$), shorter duration of neutropenia, and higher rates of consolidative therapy, but no difference in the overall survival compared with '7+3' [52]. Unfortunately, no randomized trial has been published comparing CPX-351 and FLAG or HIDAC; however, these regimens could be considered in resource-poor populations where CPX-351 is not readily available. An early phase study combining FLAG-IDA and venetoclax demonstrated early promise in both de novo and sAML but still requires more robust numbers [53].

3.2. Hypomethylating Agent (HMA)-Based Regimens

Since the FDA approvals of azacitidine in 2004 and decitabine in 2006 for the treatment of AML, they have served as the backbone of treatment for older or "unfit" adults. In recent years, they have been combined with multiple targeted agents in an effort to bolster responses and provide effective alternatives for those not receiving induction chemotherapy or as treatment for relapsed/refractory disease. Here, we will discuss some of these combinations.

3.2.1. HMA Only

5-Azacitidine was determined to be an effective in patients with AML in the AZA-PH-GL-2003 and AZA-AML-001 studies [55,56]. Fenaux et al. reported the phase 3 results (Table 2) of patients with high-risk MDS and AML with low blast count (20–30%) comparing 5-azacitidine with conventional care regimens (CCRs) at that time, namely intensive chemotherapy, low-dose cytarabine (LDAC), and best supportive care (BSC) [55]. Azacitidine significantly improved the median overall survival compared with CCRs (24.5 months vs. 16.0 months, $p = 0.005$) and was associated with fewer days spent in the hospital in a patient population with a median age of 70 years [55].

The AML-001 trial compared azacitidine with the aforementioned CCRs in adults with AML with a high-blast count (>30%) [56]. While the overall cohort did not meet statistical significance in the median OS (10.4 months vs. 6.5 months, $p = 0.1009$), the subset of patients who did not receive subsequent AML directed therapy did show an improved median OS with azacitidine compared with CCRs (12.1 months vs. 6.9 months, $p = 0.019$), which was attributed to the unbalanced use of azacitidine in the second line in CCRs regimens compared with the azacitidine arm (13.3% vs. 4.6%) with the comparable use of other agents (LDAC or decitabine) between the two arms [56].

A subsequent cytogenetic analysis of this study found significant improvement in the survival for patients with adverse cytogenetics ($-5/5q-$, $-7/7q-$, 17p abnormalities, and complex or monosomal karyotypes) [57]. The overall response [CR+CRi (complete remission with incomplete hematologic recovery)] rates were not significantly different for azacitidine (27.8%) and CCRs (25.1%).

Table 2. Hypomethylator-based frontline regimens for adults with Acute Myeloid Leukemia with an emphasis on older adults.

Study/Author	Phase/Population	Median Age (Years) [Range]	Study Medications	CR	DFS/EFS/PFS/RFS	OS
Hypomethylating Agent (HMA)-Based Regimens						
AZA-PH-GL-2003; Fenaux et al. [55]	III parallel group study, 113 adult patients (≥18 years old) with newly diagnosed AML (blast count 20–30%)	**Azacitidine**: 70 (52–80) **LDAC**: 71 (56–83) **BSC only**: 70 (56–81) **Anthracycline + Cytarabine:** 65 (50–76)	**5-Azacitidine** 75 mg/m2 on days 1–7 of 28-day cycle vs. CCRs (LDAC, BSC, or Anthracycline + Cytarabine based intensive chemo)	**Morphologic CR**: 18% vs. 16% (p = 0.80)	Not reported	**Median OS:** 24.5 mo vs. 14.6 mo HR 0.47 [0.28–0.79] (p = 0.005) **2-yr OS:** 50% vs. 16% (p = 0.001)
AZA-AML-001; Dombret et al. [56]	III parallel group study, 488 adult patients (≥65 years old) with newly diagnosed AML (blast count >30%)	**Azacitidine**: 75 (64–91) **LDAC**: 75 (65–88) **BSC only**: 78 (67–89) **Anthracycline + Cytarabine:** 60.5 (65–81)	**5-Azacitidine** 75 mg/m^2 on days 1–7 of 28-day cycle vs. CCRs (LDAC, BSC, or Anthracycline + Cytarabine based intensive chemo)	**CR + CRi**: 27.8% vs. 25.1 (all CCRs) (p = 0.5384) **CR**: 19.5% vs. 21.9% (p = 0.5766)	**Median EFS**: 6.7 mo vs. 4.6 mo (p = 0.1495) **Median RFS**: 9.3 mo vs. 10.5 mo (p = 0.5832)	**Median OS**: 10.4 mo vs. 6.5 mo (p = 0.1009) **Median OS (subset censored at time of subsequent AML therapy)**: 12.1 mo vs. 6.9 mo HR 0.76 [0.60–0.96] (p = 0.019)
NCT02203773, Dinardo et al. [58]	Ib, 57 adult patients (≥65 years old) with newly diagnosed AML who were ineligible for standard induction chemotherapy	75 (69–80)	**Venetoclax (various doses)** + HMA (Decitabine 20 mg/m^2 on days 1–5 of 28-day cycle OR 5-Azacitidine 75 mg/m^2 on days 1–7 of 28-day cycle)	**CR + CRi**: 61% **CR**: 25%	Not reported	**Median OS**: 12.3 mo
NCT02203773, Dinardo et al. [59]	Ib, 145 adult patients (≥60 years old) with newly diagnosed AML who were ineligible for standard induction chemotherapy	74 (65–86)	Same as above	**CR** + **CRi**: 67% **CR**: 37%	Not reported	**Median OS**: 17.5 mo
NCT02203773, Pollyea et al. [60]	Ib, cohort of 115 adult patients (≥65 years old) with newly diagnosed AML who were ineligible for standard induction chemotherapy	**Ven + AZA**: 75 (61–90) **Ven + Dec**: 72 (65–86)	**Venetoclax** 400 mg PO daily + HMA (Decitabine 20 mg/m^2 on days 1–5 of 28-day cycle OR 5-Azacitidine 75 mg/m^2 on days 1–7 of 28-day cycle)	**Ven+AZA** **CR + CRi**: 71% **CR**: 44% **Ven+Dec** **CR + CRi**: 74% **CR**: 55%	Not reported	**Ven+AZA** **Median OS**: 16.4 mo **Ven+Dec** **Median OS**: 16.2 mo

Table 2. *Cont.*

Study/Author	Phase/Population	Median Age (Years) [Range]	Study Medications	CR	DFS/EFS/PFS/RFS	OS
VIALE-A; Dinardo et al. [61]	III, 431 adult patients (≥18 years old) with newly diagnosed AML who were ineligible for standard induction chemotherapy	76 (49–91) **AZA + Ven:** 76 (49–91) **AZA + Placebo:** 76 (60–90)	5-Azacitidine + **Venetoclax** 400 mg PO daily vs. 5-Azacitidine + Placebo	**CR + CRi:** 66.4% vs. 28.3% ($p < 0.001$) **CR**: 36.7% vs. 17.9% ($p < 0.001$)	**Median EFS:** 9.8 mo vs. 7.0 mo HR 0.63 [0.50–0.80] ($p < 0.001$)	**Median OS:** 14.7 mo vs. 9.6 mo HR 0.66 [0.52–0.85] ($p < 0.001$)
DACO-016; Kantarjian et al. [62]	III, 485 adult patients (≥65 years old) with newly diagnosed AML who were ineligible for standard induction chemotherapy	73 (64–91) **Decitabine**: 73 (64–89) **BSC**: 75 (66–86) **LDAC**: 73 (64–91)	**Decitabine** 20 mg/m^2 on days 1–5 of 28-day cycle vs. BSC/LDAC	**CR + CRp**: 17.8% vs. 7.8% OR 2.5 [1.4–4.8] ($p = 0.001$) **CR + CRi + CRp**: 27.7% vs. 10.6% **CR**: 15.7% vs. 7.4%	Not reported	**Median OS (planned analysis)**: 7.7 mo vs. 5.0 mo ($p = 0.108$) **Median OS (unplanned analysis)**: 7.7 mo vs. 5.0 mo HR 0.82 [0.68–0.99] ($p = 0.037$)
NCT03404193; Maiti et al. [63]	II, cohort of 12 adult patients (>60 years old) with newly diagnosed AML	70 (69–78)	5-day Decitabine + FLT3 inhibitor + Venetoclax	**CR + CRp + CRi**: 92% **CR**: 75%	**18-mo PFS**: 59% **Median PFS**: Not reached	**2-yr OS**: 80% **Median OS**: Not reached
NCT00492401; Blum et al. [64]	II, adult patients (≥60 years old) with newly diagnosed AML who were ineligible for or refused standard induction chemotherapy	74 (60–85)	**Decitabine** 20 mg/m^2 on days 1–10 of 28-day cycle	**CR**: 47%	**Median DFS**: 46 wks	**Median OS**: 55 wks
Ritchie et al. [65]	52 adult patients (>60 years old, included 2 patients under 60 with numerous comorbidities) with newly diagnosed AML	75 (45–91)	**Decitabine** 20 mg/m^2 on days 1–10 of 28-day cycle	**CR**: 40%	Not reported	**Median OS**: 318 days
NCT01687400; Welch et al. [66]	II, 116 adult patients with newly diagnosed AML (≥60 years old), relapsed AML (≥18 years old), or transfusion-dependent AMS	74 (29–88)	10-day **Decitabine**	**CR + CRi**: 34% **CR**: 13%	Not reported	**Median OS**: **Unfav Risk** 11.6 mo **Fav/Int Risk** 10.0 mo **TP53 Mutants** 12.7 mo **TP53 Wild Type** 15.4 mos
Dinardo et al. [67]	II, cohorts with a total of 85 adult patients (≥60 years old) with newly diagnosed AML or untreated sAML who were ineligible for standard induction chemotherapy	72 (68–78)	10-day **Decitabine** + **Venetoclax** 400 mg PO daily	**CR** + **CRi**: 81% **CR**: 61%	Not reported	**Median OS for newly diagnosed AML**: 18.1 mo **Median OS for untreated sAML**: 7.8 mo

Table 2. *Cont.*

Study/Author	Phase/Population	Median Age (Years) [Range]	Study Medications	CR	DFS/EFS/PFS/RFS	OS
Maiti et al. [68]	Retrospective propensity-score matched, 170 adult patients with newly diagnosed AML	**10-day Decitabine + Venetoclax**: 72 (69–78) **Intensive chemotherapy**: 73 (67–76)	10-day **Decitabine** + **Venetoclax** 400 mg PO daily vs. intensive chemotherapy containing at least cytarabine ≥ 1 g/m^2/d in combination with other agents	**CR** + **CRi**: 81% vs. 52% OR 3.78 [1.81–7.88] ($p < 0.001$) **CR**: 62% vs. 42% OR 2.21 [1.18–4.16] ($p = 0.01$)	**Median EFS**: 9.0 mo vs. 2.3 mo HR 0.47 [0.33–0.67] ($p < 0.0001$)	**Median OS**: 12.4 mo vs. 5.0 mo OR 0.48 [0.29–0.79] ($p < 0.01$)
Nand et al. [69]	II, 20 adult patients (≥56 years old) with newly diagnosed AML or RAEB-I or RAEB-II MDS	76 (64–83)	**Azacitidine** 75 mg/m^2 on days 1–7 and **Gemtuzumab ozogamicin** 3 mg/m^2 on day 8 of 28-day cycle + Hydroxyurea (to lower WBC count)	**CR** + **CRi**: 70% **CR**: 55%	Not reported	**Median OS**: 11 mo
NCT00658814; Nand et al. [70]	II, 142 adult patients (≥60 years old) with newly diagnosed AML Favorable risk: 60–69 years old or Zubrod PS 0 or 1 (83 pts) Adverse risk: ≥70 years old AND Zubrod PS 2–3 (59 pts)	**Favorable Risk** 71 (60–88) **Adverse Risk** 75 (70–87)	**Azacitidine** 75 mg/m^2 on days 1–7 and **Gemtuzumab ozogamicin** 3 mg/m^2 on day 8 of 28-day cycle+ Hydroxyurea (to lower WBC count)	**Favorable Risk** **CR + CRi**: 44% **CR**: 28% **Adverse Risk** **CR + CRi**: 35% **CR**: 20%	**Favorable Risk** **Median RFS**: 8.3 mo **Adverse Risk** **Median RFS**: 7 mo	**Adverse Risk** **Median OS**: 11 mo **AdverseRisk** **Median OS**: 11 mo
NCT02677922; Dinardo et al. [71]	Ib, cohort of 23 adult patients (≥18 years old) with newly-diagnosed, mutant *IDH1* AML ineligible for induction chemotherapy	76 (61–88) 52% ≥75 yrs	5-AZA 75 mg/m^2 on days 1–7 + **Ivosidenib** 500 mg daily every 28-day cycle	**CR + CRh** 69.6% **CR** 60.9%		**Median OS** Not reached **12-mo OS** 82%
NCT02677922 (ASH 2019); Dinardo et al. [72]	I/II, cohort of 101 adult patients (≥18 years old) with newly-diagnosed, mutant *IDH2* AML ineligible for induction chemotherapy	74 (62–85)	5-AZA 75 mg/m^2 on days 1–7 + **Enasidenib** 100 mg daily every 28-day cycle vs. 5-AZA 75 mg/m^2 on days 1–7 of 28-day cycle	**ORR** 68% vs. 42% ($p = 0.0155$) **CR** 50% vs. 12% ($p = 0.0002$)	Not reported	Not reported
NCT02677922 (ASCO 2020); Dinardo et al. [73]	Updated results from phase I/II study above	75 (57–85)	Same as above	**ORR** 71% vs. 42% ($p < 0.01$) **CR** 53% vs. 12% ($p < 0.01$)	**Median EFS** 17.2 vs. 10.8 mo HR 0.59 [0.30–1.17] ($p = 0.13$)	**Median OS** 22 mo [both arms]

The role of decitabine in AML was established in the DACO-016 trial [62]. While 5-day decitabine did not show a significant improvement in the median OS (7.7 months vs. 5.0, $p = 0.108$), it did result in an improved CR + CRp (complete remission without platelet recovery) rate (17.8% vs. 7.8%, $p = 0.001$) compared with LDAC or BSC [62].

While these served as good palliative options, they were limited in their ability to achieve CR and did not produce sustained remissions following treatment cessation. Thus, additional agents were needed to achieve higher remission rates in the hopes of longer remissions and perhaps even consolidation with allogeneic stem cell transplantation.

One approach studied to improve responses to HMAs was the prolongation of decitabine administration, from 5 days to 10 days. In newly-diagnosed AML, this has led to promising improvement in response rates and survival [64]. One study that included over 50% sAML, 10-day decitabine resulted in a CR rate of 40% with a median OS of 318 days [65]. Another study reported favorable results in adverse risk AML, particularly *TP53*-mutated disease. ORR in adverse risk was significantly better than intermediate or favorable-risk disease for those treated with 10-day decitabine (67% vs. 34%, $p < 0.001$) [66]. Moreover, *TP53*-mutated AML had a better ORR than *TP53*-wild type disease (100% vs. 41%, $p < 0.001$) [66]. This presents a novel option for a patient population with a historically poor prognosis.

3.2.2. HMA-Venetoclax

BCL-2 is part of a family of intracellular proteins that inhibit the intrinsic apoptotic pathway for cellular death [74]. The inhibition of BCL-2 was found to result in apoptosis of leukemic blasts in vitro and in pre-clinical models leading to further evaluation [74]. This eventually led to phase 1b dose-escalation studies combining decitabine or azacitidine with the BCL-2 inhibitor, venetoclax, in patients age 65 and older with newly diagnosed AML that showed encouraging activity and tolerability [58,59]. The combination of azacitidine and venetoclax had a median CR/CRi duration of 21.9 months and median OS of 16.4 months with largely grade 3 cytopenias and febrile neutropenia rate of 39%.

The smaller cohort who received a combination of decitabine and venetoclax had a median CR/CRi duration of 15.0 months and median OS of 16.2 months with similar cytopenias and a febrile neutropenia rate of 65% [60]. It led to this combination receiving accelerated approval from the FDA in 2018 and subsequent confirmatory studies. VIALE-A is the phase 3, 2:1 randomized study comparing azacitidine and venetoclax (400 mg daily) with azacitidine and placebo [61].

The median age of the study population was 76 years, and the median OS was significantly greater for azacitidine and venetoclax (14.7 months vs. 9.6 months, $p < 0.001$) [61]. The combination resulted in over a doubling of the CR rate (36.7% vs. 17.9%, $p < 0.001$) and CR/CRi rate (66.4% vs. 28.3%, $p < 0.001$) [61]. Nausea, febrile neutropenia, and grade 3 cytopenias were the predominant toxicities seen with therapy [61]. This has now become the standard of care for patients unfit for intensive chemotherapy with newly diagnosed AML [1].

One variation that produced higher response rates in newly diagnosed, intensive chemotherapy ineligible, AML was 10-day decitabine. Dinardo et al. reported a phase 2 study of 10-day decitabine combined with venetoclax for de novo, secondary, and relapsed/refractory AML with a median age of 71 years and with 30% of enrolled patients with ECOG PS of 2 or more [67]. ORR were 74% for the entire cohort, 89% for de novo AML, and 80% for untreated sAML with median OS of 18.1 months and 7.8 months, respectively [67]. The median age of treated patients was 72 years old, and 64% had adverse risk disease by ELN classification [75].

However, this treatment presented high, but manageable, rates of toxicity, including 47% grade 3 or 4 neutropenia, 38% neutropenic fever, 83% of patients with serious adverse events, and a 3.6% 30-day mortality [67]. The impact of measurable residual disease (MRD) on prognosis was also assessed for this combination. The median time to MRD-negativity was two (2) months, and the median OS was significantly longer for patients achieving MRD-negativity by one (1) month compared with those who were MRD-positive (25.1

months vs. 3.4 months, $p < 0.0001$) [75]. MRD-negativity by two (2) months was associated with longer median EFS (not reached [NR] vs. 5.8 months, $p < 0.001$), median RFS (NR vs. 5.2 months, $p = 0.004$), and median OS (25.1 months vs. 7.1 months, $p < 0.001$) compared with patients with MRD-positivity [75].

Lastly, MRD-negative CR was associated with longer median OS than lesser responses (25.1 months vs. 11.6 months, $p < 0.0005$) [75]. A propensity-matched retrospective study compared patients treated with 10-day decitabine and venetoclax on the phase 2 study with "intensive chemotherapy" (regimens containing 1 g or more of cytarabine either alone or in combination) [68]. The median age of the study population was 72 years and treatment with 10-day decitabine and venetoclax was associated with lower rates of relapse, lower 30-day mortality, higher CR/CRi rates, and longer survival [68]. The combination of 10-day decitabine and venetoclax is also being studied with the addition of FLT3 inhibitors in *FLT3*-mutated AML [63].

3.2.3. HMA-IDH Inhibitors

Isocitrate dehydrogenase 1 and *2* (*IDH1* and *IDH2*) mutations are present in roughly 5–10% and 10–20% of patients newly diagnosed AML, respectively [9,72,76,77]. Its frequency makes it a particularly appealing target in patients who are unfit for intensive treatment. Given the early promising data reporting the benefits of both ivosidenib (IDH1-inhibitor) and enasidenib (IDH2-inhibitor) in relapsed disease, these two drugs are under investigation in combination with azacitidine for frontline treatment [71–73]. The early phase results for the combination of IDH-inhibitors and azacitidine are promising and are under further investigation in phase 3 (AGILE and IDHENTIFY) studies.

Further use of precision medicine in older patients with newly diagnosed AML based on genomic profiling is under evaluation in the BEAT AML trial with early results showing feasibility of initiating treatment within seven (7) days [78].

3.3. Other Treatment Approaches, Including Targeted Onotherapy or Other Combinations

While hypomethylating agents with or without venetoclax are used to treat the majority of older or "unfit" adults, there are several other agents that may be used in patients who are unable to receive these therapies or those with relapsed/refractory disease.

3.3.1. LDAC +/− Glasdegib

Low-dose cytarabine (Ara-C) was compared to BSC with hydroxyurea in patients with AML or MDS unfit for intensive treatment, largely over the age of 60 years (median age 74 years). LDAC resulted in better CR rates (18% vs. 1%, $p = 0.00006$) and overall survival (Table 3) [79]. This led to the approval for LDAC as an alternative for patients unfit for intensive treatment. Later, the addition of glasdegib, a Hedgehog pathway inhibitor, was evaluated for the treatment of patients with AML or high-risk MDS with a median age of 76 years [80]. The median overall survival (8.8 months vs. 4.9 months, $p = 0.0004$) and CR rates (17% vs. 2.3%, $p < 0.05$) were better with LDAC and glasdegib than with LDAC alone [80].

Table 3. Other non-intensive non-hypomethylator-based frontline regimens for patients with AML.

Study/Author	Phase/Population	Median Age (Years) [Range]	Study Medications	CR	DFS/EFS/PFS/RFS	OS
			Other Agents			
EORTC-GIMEMA AML-19; Amadori et al. [81]	III, 237 adult patients (>60 years old) with newly diagnosed AML	**Overall**: 77 (62–88) **GO**: 77 (62–88) **BSC**: 77 (66–88)	**GO** 6 mg/m^2 on day 1, 3 mg/m^2 on day 8, followed by 2 mg/m^2 monthly (up to 8 months) vs. BSC (Hydroxyurea could be used in BSC arm only)	**CR + CRi**: 27% **CR**: 8.1%	**Median PFS**: 2.8 mo (GO arm only)	**Median OS**: 4.9 mo vs. 3.6 mo HR 0.69 [0.53–0.90] (p = 0.005) **1-yr OS**: 24.3% vs. 9.7%
NCRI AML-14; Burnett et al. [79]	Cohort of 217 adult patients with newly diagnosed AML or high-risk MDS (>10% BM blasts) who were deemed unfit for intensive chemotherapy by local investigator	74 (51–90) 4 patients <60 years old and 165 patients >70 years old	**LDAC** 20 mg BID for 10 days every 28–42 days vs. BSC (Hydroxyurea) Both arms were also randomized to receive or not receive ATRA for 60 days	**CR**: 18% vs. 1% OR 0.15 [0.06–0.37] (p < 0.00006)	Not reported	Median not reported OR 0.60 [0.44–0.81] (p = 0.0009)
NCT01546038; Cortes et al. [80]	II, 132 adult patients (≥55 years old) with newly diagnosed AML (116 pts) or high-risk MDS who were ineligible for standard induction chemotherapy	**LDAC + Glasdegib**: 77 (63–92) **LDAC alone**: 75 (58–93)	LDAC 20 mg BID for 10 days of every 28-day cycle + **Glasdegib** 100 mg PO daily vs. LDAC 20 mg BID for 10 days of every 28-day cycle	**CR**: 17% vs. 1% (p = 0.0142)	Not reported	**Median OS:** **All:** 8.8 mo vs. 4.9 mo HR 0.513 [0.394–0.666] (p = 0.0004) **AML cohort**: 8.3 mo vs. 4.3 mo HR 0.46 [0.35–0.62] (p = 0.0002)
NCT02287233; Wei et al. [82]	Ib/II, 82 adult patients (≥60 years old) with previously untreated AML who were ineligible for intensive chemotherapy 49% sAML	74 (63–90)	LDAC 20 mg BID for 10 days + **Venetoclax** 600 mg PO daily every 28-day cycle	**CR + CRi**: 54% **CR**: 26%	Not reported	**Median OS**: 10.1 mo
VIALE-C; Wei et al. [83]	III, 211 adult patients (≥18 years old) with newly diagnosed AML who were ineligible for intensive chemotherapy with 2:1 randomization **sAML**: 41% vs. 34%	76 (36–93) **Venetoclax arm**: 76 (36–93) **Placebo arm**:76 (41–88)	LDAC 20 mg BID for 10 days + **Venetoclax** 600 mg PO daily every 28-day cycle vs. LDAC 20 mg BID for 10 days + Placebo	**CR + CRi**: 48% vs. 13% (p < 0.001) **CR + CRh**: 47% vs. 15% (p < 0.001) **CR**: 27% vs. 7% (p < 0.001)	**Median EFS**: 4.7 mo vs. 2.0 mo (p = 0.002)	**Pre-planned Median OS analysis**: 7.2 mo vs. 4.1 mo HR 0.67 [0.47–0.96] (p = 0.03) **Additional 6-mo follow-up Median OS analysis**: 8.4 mo vs. 4.1 mo HR 0.70 [0.50–0.99] (p = 0.04)
Scappaticci et al. [84]	Retrospective case-control study, adult patients (≥60 years old) with newly diagnosed AML who were ineligible for standard induction chemotherapy	**Clofarabine**: 72.7 (60.7–80.9) **FLAG**: 70.2 (60.1–83.0)	Clofarabine vs. FLAG	**CR + CRi**: 65.6% vs. 37.5% (p = 0.045) **CR**: 56.3% vs. 31.3% (p = 0.077)	**Median EFS**: 7.0 mo vs. 2.8 mo (p = 0.110)	**Median OS**: 7.9 mo vs. 2.8 mo (p = 0.085)

3.3.2. Venetoclax +/− LDAC

Venetoclax has also been evaluated as a monotherapy (800 mg daily) in patients with relapsed/refractory disease or those who are unfit for intensive chemotherapy. In a phase 2 study of 32 patients (median age 71 years) with 94% having received prior therapy (including 75% receiving prior HMA), the CR/CRi rates were 19% with a median leukemia-free survival (LFS) of 2.3 months, median OS of 4.7 months, and more favorable results in *IDH*-mutated AML [85]. The combination of venetoclax and LDAC was granted accelerated approval by FDA in 2018 based on the results of the phase 1b/2 study reporting a 44% CR/CRi rate and median OS of 10.1 months [82].

This led to the VIALE-C trial, a phase 3, 2:1 randomized trial comparing LDAC and placebo with LDAC and venetoclax (600 mg daily dose). Unfortunately, LDAC and venetoclax did not result in a significant improvement in the median OS (7.2 months vs. 4.1 months, $p = 0.11$) at the time of pre-planned analysis; however, with an unplanned additional 6-months of follow-up, significant improvement in the median OS was seen with the combination (8.4 months vs. 4.1 months, $p = 0.04$) [83]. The combination also resulted in higher CR/CRi rates, including a 27% CR rate, compared with LDAC monotherapy (48% vs. 13%, $p < 0.001$) [83].

3.3.3. GO +/− HMA

Gemtuzumab ozogamicin (GO), is a CD33-monoclonal antibody combined with calcheamicin (DNA intercalator), which was first approved in 2000 for the treatment of relapsed/refractory AML in unfit patients. It has had a tumultuous history, particularly in elderly patients [86]. Following its approval, it was studied in combination with azacitidine. In a pilot study by Nand et al., azacitidine, GO, and hydroxyurea resulted in a 40% CR/CRi rate with a median survival of 10 months in an elderly patient population (median age 76 years) [69]. A phase 2 study published in 2013 reported on the combination of azacitidine and GO and noted a CR/CRi rate of 44% in its favorable-risk cohort (median age 71 years) and 35% in its adverse-risk cohort (median age 75 years) [70].

Furthermore, the median RFS was 8 months in the favorable-risk cohort and 7 months in the adverse-risk cohort, with an OS of 11 months in both groups [70]. The EORTC-GIMEMA AML-19 trial was a phase 3 study comparing BSC to GO in patients over 60 years old with newly diagnosed AML who were unfit for intensive chemotherapy. GO was found to improve the median OS compared with BSC (4.9 months vs. 3.6 months, $p = 0.005$) [81]. GO monotherapy could be considered in patients who are not fit to tolerate HMA or LDAC combinations discussed above.

Clofarabine, a nucleoside analog, has been studied retrospectively in older patients ineligible for induction chemotherapy with promising results [84].

4. Consolidation Treatment

While most patients treated with induction chemotherapy have a complete remission, durability following treatment was an early issue with intensive therapy until post-remission, or consolidation, treatments were studied and found to be beneficial in sustaining these responses and potentially resulting in long-term cure. Consolidation is often achieved with either chemotherapy alone or with chemotherapy followed by hematopoietic stem cell transplantation.

4.1. Chemotherapy

Post-remission chemotherapy, namely with the use of varying doses of cytarabine was initially utilized following small, uncontrolled studies in the early 1980s and was solidified as a mainstay for post-remission therapy following intensive induction since the publication of CALGB-8525 in 1994. However, the optimal dose, cycles, and timing of cytarabine administration are not entirely clear. Furthermore, many of these studies were performed in younger patients while the benefits in older, yet "fit" patients is somewhat murkier. While CALGB-8525 (Table 4) did include a large number of patients over 60 years

old, only 29% were able to complete the four courses of high-dose cytarabine (HIDAC), at a dose of 3 g/m^2, compared with 66% completing courses of 400 mg/m^2 continuous infusion cytarabine [23].

While HIDAC resulted in prolonged survival in the entire studied cohort and subgroup of patients under 60 years old, it did not improve survival in those over 60 years old [23]. Later analyses of this study also found that patients with a normal karyotype, core-binding factor (CBF), and those with *RAS*-mutated, non-CBF AML had a lower incidence of relapse with HIDAC [87,88]. A lower dose (2 g/m^2) was evaluated via a single institution study without a comparator arm in older patients with good tolerability [89]. Furthermore, a modified intermediate-dose cytarabine (IDAC, 1 g/m^2 every 12 h for 5 days) was compared to HIDAC as part of a multiagent treatment regimen in Japan and resulted in similar outcomes and less hematologic toxicity [90].

However, given the complexity of the treatment schedule and multiagent approach, it is difficult to extrapolate these results to patients receiving single-agent cytarabine as a consolidation treatment. An alternative dosing schedule HIDAC has shown promise in young patients with quicker hematologic recovery, less days in the hospital, lower infection rates and no difference in survival with or without co-administration of pegfilgrastim compared with standard HIDAC dosing [91]. Further evaluation in additional randomized trials amongst older patients is needed. Notably patients treated with HMA and venetoclax do not typically undergo consolidation chemotherapy and instead remain on HMA/venetoclax as long as the response continues or toxicities are not seen.

Table 4. Consolidation regimens for adults with AML with an emphasis on older adults.

Study/Author	Phase/Population	Median Age (Years) [Range]	Medications	CR + CRi/CR	DFS/EFS/PFS/RFS	OS
CALGB-8525; Mayer et al. [10]	III, 1088 patients (≥16 years old) with newly diagnosed primary AML who received intensive induction chemotherapy 596 adult patients in CR went on to be randomized to one of three post-remission cytarabine doses	52 (16–86) 32% patients were >60	All patients received induction with 7-days of continuous cytarabine 200 mg/m^2 infusion and 3-days of bolus daunorubicin (45 mg/m^2 for ≤60 years old and 30 mg/m^2 for >60 years old) Patients in CR after induction were randomized to **one of three Cytarabine regimens (four 28-day cycles)**: (1) 100 mg/m^2 continuous infusion for 5 days (2) 400 mg/m^2 continuous infusion for 5 days (3) 3 g/m^2 over 3h q12h on days 1,3,5	**After Induction CR** **<40 yrs**: 75% **40–60 yrs**: 68**>60 yrs**: 47%	**4-yr DFS (pts who received consolidation)** **All**: 21% vs. 25% vs. 39% (p = 0.003) **Stratified by age** **<40 yrs**: 32% **40–60 yrs**: 29% **>60 yrs**: 14% (p < 0.001) **Over 60 yrs** (n = 129): 16% or less for all three doses (p = 0.19)	**4-yr OS (entire study)** **Stratified by Age:** **<40 yrs**: 38% **40–60 yrs**: 27% **>60 yrs**: 9% (p < 0.001) **4-yr OS (pts who received consolidation)** **All**: 31% vs. 35% vs. 46% (p = 0.04) HR 0.74 [0.57–0.96] (for 3 g/m^2 vs. 100 mg/m^2) HR 0.78 [0.61–1.00] (for 400 mg/m^2 vs. 100 mg/m^2)
Sperr et al. [67]	79 adult patients (≥60 years old) with de novo AML of whom 49 patients had CR following intensive induction chemotherapy at a single institution	70 (60–89)	Cytarabine 2 g/m^2 over 3 h q12 h on days 1, 3, 5 every 28-days for 4 cycles	**CR (after induction)** 62% **Median Continuous CR (CCR)** 15.9 mo **5-yr CCR** 30%	**Median DFS** 15.5 mo **5-yr DFS** 22%	**Median OS (all pts)** 10.6 mo **5-yr OS (all pts)** 18% **Median OS (consolidation pts)** 31.8 mo **5-yr OS (consolidation pts)** 34%
Fukushima et al. [75]	26 adult patients (≥18 years old) with newly diagnosed AML 21 of these patients were randomized to HIDAC or modified IDAC (mIDAC)	**HIDAC Arm** 48 (26–43) **mIDAC Arm** 50 (20–64)	Multiagent chemotherapy including remission-induction, consolidation, and intensification regimens containing two cycles of either: HIDAC 2 g/m^2 q12h on days 1–5 or **mIDAC** 1 g/m^2 q12h on days 1–5	**CR** 84.6%	**4-yr RFS** 49% vs. 56% (p = 0.86)	Not reported
AMLSG 07–04; Jaramillo et al. [68]	II/III, 568 adult patients (18–60 years old) with newly diagnosed AML in CR cohorts after induction with ICE chemotherapy ± ATRA	**German Intergroup Arm** 41.6 (19–60) **HIDAC 123 Arm** 47.7 (18–61) **HIDAC 135 Arm** 47.6 (18–61)	**HIDAC** 3 g/m^2 q12 h on days 1–3 with pegfilgrastim vs. days 1, 3, 5 with or without pegfilgrastim (Standard German Intergroup Arm)	Not applicable	**2-yr RFS** 50% vs. 51% **4-yr RFS** 41% vs. 46% **6-yr RFS** 40% vs. 44% (p = 0.48)	**2-yr OS** 75% vs. 74% **4-yr OS**62% vs. 64% **6-yr OS** 60% vs. 59% (p = 0.90)

4.2. Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation, including both allogeneic (allo-SCT) and autologous stem cell transplantation (ASCT), remains a potentially curative option for fit, older patients. Since 2000, there have been growing numbers of older patients undergoing allo-SCT [92]. Survival has also improved with allo-SCT, although inferior outcomes were seen with myeloablative conditioning [92]. Age does not have a negative influence on transplant outcomes [93–95]. Much of the data on allo-SCT in elderly patients is from retrospective or small, early-phase studies evaluating everything from the intensity of conditioning regimens to stem cell sources and donor–recipient characteristics [96–104].

Reduced-intensity conditioning provides an avenue for allo-SCT in older patients with lower TRM and LFS, higher relapse rates, and similar overall survival [104,105]. Allo-SCT with a HLA-matched donor, particularly from a sibling donor, appears to be a more effective consolidation method than autologous stem cell transplantation (auto-SCT) [106–108]. Although relapses are more common with auto-SCT, it is associated with lower treatment-related mortality and similar overall survival [106–109]. Auto-SCT remains a safe and effective consolidation approach in some older AML patients who do not have a readily available donor [110,111].

5. Maintenance Treatment

Since many patients are unable to safely undergo curative intent treatment, and even those who can endure these initial treatments, they are often unable to undergo further intensive therapies in the event of relapse. Thus, effective and tolerable post-remission maintenance treatments are paramount in improving the survival and remission for these patients. Several approaches have been studied, with and without stem cell transplantation. The use of hypomethylating agents has shown promise in this space. HOVON-97 evaluated the role of subcutaneous azacitidine (50 mg/m^2 on days 1–5 of 28-day cycle for 12 cycles) as maintenance therapy following at least two cycles of intensive chemotherapy for AML in older patients (Table 5) [112].

Although azacitidine maintenance did not improve the OS it did improve the DFS [112]. Unfortunately, when azacitidine was studied in patients as a maintenance treatment after receiving allogeneic stem cell transplantation, it did not result in improved RFS or OS [113]. More recently, QUAZAR AML-001 studied the use of oral azacitidine (CC-486 300 mg daily for days 1–14 of 28-day cycle) as a maintenance treatment for older patients in first remission after intensive treatment [114]. CC-486 improved not only the RFS but also the OS without detrimental effects on quality of life [114]. Given the durable benefits of therapies affecting the immune system, such as allogeneic stem cell transplantation, there has been hope regarding the role of immune checkpoint inhibitors.

An early phase study of nivolumab maintenance in patients with high-risk AML who were not undergoing allogeneic stem cell transplantation showed an RFS comparable to historical observations but a promising OS, thus, prompting evaluation as part of combination therapy for patients with high-risk AML [115]. Optimal maintenance strategies need to be determined for older patients who are limited in their ability to receive intensive treatments upon relapse of their disease.

Table 5. AML maintenance regimens with an emphasis on older adult outcomes.

Study/Author	Phase/Population	Median Age (Years) [Range]	Medications	DFS/EFS/PFS/RFS	OS
HOVON97; Huls et al. [112]	III, 116 adult patients (≥60 years old) with newly diagnosed AML or MDS-RAEB in CR/CRi after at least 2 cycles of intensive chemotherapy	69 (60–81)	5-AZA SC 50 mg/m^2 on days 1–5 of 28-day cycle (max 12 cycles) vs. observation	**Median DFS** 15.9 mo vs. 10.3 mo HR 0.62 [0.41–0.95] (p = 0.026) **12-mo DFS** 64% vs. 42% (p = 0.04)	**12-mo OS** 84% vs. 70% (p = 0.69) HR 0.91 [0.58–1.44] (p = 0.69)
QUAZAR AML-001; Wei et al. [114]	III, 472 adult patients (≥55 years old) with AML in CR/CRi after induction chemotherapy with or without consolidation and were not being evaluated for allo-SCT	68 (55–86)	CC-486 (oral form of azacitidine) 300 mg PO vs. placebo PO daily for days 1–14 of 28-day cycle	**Median RFS** 10.2 mo vs. 4.8 mo (p < 0.001)	**Median OS** 24.7 mo vs. 14.8 mo (p < 0.001)

Table 5. *Cont.*

Study/Author	Phase/Population	Median Age (Years) [Range]	Medications	DFS/EFS/PFS/RFS	OS
NCT00887068; Oran et al. [113]	I/II, 187 adult patients (18–75 years old) with AML/MDS in CR with "high-risk features" between 42–100 days after allo-SCT	**AZA arm:** 57 (19–72) **Obs arm:** 57.5 (20–75)	SC 5-AZA 32 mg/m^2 on days 1–5 vs. of 28-day cycle (max 12 cycles) vs. observation	**Median RFS** 2.07 yr vs. 1.28 yr (p = 0.43) HR 0.73 [0.49–1.1] (p = 0.14)	**Median OS** 2.52 yr vs. 2.56 yr (p = 0.85) HR 0.84 [0.55–1.29] (p = 0.43)
Reville et al. [115]	II, 15 adult patients (≥18 years old) with "high-risk" AML in CR/CRi/PR who were not being considered for allo-SCT	56(31–71)	Nivolumab 3 mg/kg IV q2w for 6 cycles then q4w for cycles 7–12, then q3mo after cycle 12	**Median RFS** 8.48 mo **6-mo RFS** 57.1%	**Median OS** Not reached

6. Measurable Residual Disease (MRD)

Measurable (previously minimal) residual disease has been a developing area of study over the last decade with significant clinical implications, and its assessment after completion of intensive therapy has even been included in recent guidelines [1,116]. Given the potential for sampling error or variation in bone marrow evaluation for morphologic evidence of persistent leukemia during or after treatment, more sensitive approaches were developed and studied [117]. The ability to detect the presence of minute numbers of cells (at least 1:10,000 and even 1:100,000) by one of three methods, multiparameter flow cytometry (MFC), next-generation sequencing (NGS), or reverse-transcriptase quantitative polymerase chain reaction (RT-qPCR) has been found to be prognostic and in other diseases (such as ALL) prompts initiation of specific alternate therapies [118–123].

Cytotoxic, targeted, and cellular therapies can lead to alterations and evolution in the molecular and genomic characteristics of any residual disease, emphasizing the importance of inclusion of NGS testing at some interval after these treatments to potentially guide future treatment options [124,125]. Additional studies are assessing combinations of these methods at various time points in the disease course and with different samples (peripheral blood vs. bone marrow) [126,127].

7. Supportive Care

The treatment of elderly patients with AML is fraught with difficulties for the patient, caregivers and providers. Palliative and supportive care have been shown to play a significant role in the optimal management of patients with malignancies; however, several barriers are thought to exist regarding its integration into the management of hematologic malignancies [128].

Role of Integrated Palliative Care

Palliative care in hematologic malignancies is paramount for maintaining quality of life (QOL) and tolerating treatment, emotional stress, managing toxicities, and for survivorship in the elderly [129]. However, palliative care clinicians may lack adherence to quality measures in symptom assessment and meeting the emotional needs in patients with hematologic malignancies, compared to those with solid tumors [130]. Palliative care support is on the rise over the last decade in hematologic malignancies [131]. When integrated into the care of a patient with AML, palliative care improves QOL and decreases depression as well as post-traumatic stress disorder (PTSD) symptoms with effects lasting more than 6 months [132]. Yet early palliative care (>30 days prior to death) is often still lacking, with a median time from first palliative care encounter to death of 10 days [131].

8. Future Directions

AML is often a disease of older adults in the United States, many of which have multiple medical comorbidities and are often able to tolerate limited, if any, intensive therapy. There are a number of novel approaches currently being investigated, ranging from small molecule inhibitors, targeted agents, and cellular therapies targeted at engaging the immune system to destroy previously veiled leukemic cells. Uproleselan (GMI-1271), a

novel E-selectin antagonist, is perhaps the furthest along in the drug development pathway and is currently under phase 3 evaluation in both frontline and relapsed/refractory AML in combination with chemotherapy [133,134].

With the prevalence and poor outcomes of *TP53*-mutated AML, targeting p53 has been of paramount importance in AML. Eprenetapopt (APR-246), a novel intravenous infusion that causes p53 re-conformation, in turn reactivating its cell cycle arrest and proapoptotic functions is currently being studied in combination with azacitidine with promise in early studies [135,136]. There are a number of different approaches being studied that aim to enhance host immune response with either bispecific antibodies, or cellular therapies, namely chimeric antigen receptor T-cells (CAR-T) or donor leukocyte infusion (DLI) [137–147]. Current bispecific constructs that are in various stages of evaluation include CD3-FLT3, CD3-CD33, and CD3-CD123 [143–147].

Some current targets for CAR-T therapy include CD13 and TIM3, CD33, CD34, CD38, CD56, CD70, CLL1, CD117, and CD123 [138–142]. We remain hopeful that, over the next few years, continued advancement in the understanding of the biology of AML and an emphasis on development of precision medicine approaches will produce effective, tolerable, and potentially curative approaches for patients unable to undergo treatment with intensive therapies.

9. Conclusions

AML is a heterogenous clonal disorder that hijacks normal hematopoiesis in order to promote its own malignant survival. The incidence of AML increases with advancing age with the bulk of patients who develop AML being 60 years of age or older. Historically these older AML patients have been treated like their younger counterparts with high intensity induction chemotherapy. The biology of AML in older adults, however, is not like in younger patients due to an enrichment for adverse risk cytogenetic and molecular mutations, namely monosomal karyotypes, complex cytogenetics, *ASXL1* mutations, and *p53* mutations, which confer inherent resistance to traditional cytotoxic chemotherapy. Advancing age also brings with it additional medical co-morbidities and varying levels of fitness that must be taken into account prior to the initiation of therapy.

Fitness, with some caveats, such as *p53* mutations, continues to be the main determining factor in patient selection for intensive induction chemotherapy. Patients with core binding factor leukemia and *NPM1* mutations with normal karyotypes should also be considered for induction chemotherapy given the curative potential. Most older AML patients, however, will not have favorable genetic risk. Fortunately, new therapies, such as hypomethylators and venetoclax, have arisen that confer morphologic remission and survival rates equal to or better than those of intensive chemotherapy.

These treatments can be given as outpatient therapy, do not have the same level of toxicities as intensive chemotherapy, and are tolerated with dose attenuation across the age spectrum of older adults with AML. Additional targeted therapies are in development to precisely block mutational pathways that are essential to leukemic cell survival. Additional work is required to improve the initial response rates for all older AML subgroups. Better consolidative/maintenance strategies that focus on MRD endpoints to lessen the time in therapy and to improve the overall survival are still sought underscoring the ongoing trials and tribulations of frontline therapy in older AML.

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