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Advances in non-intensive chemotherapy treatment options for adults diagnosed with acute myeloid leukemia

Elizabeth A. Griffiths[a,*], Hetty E. Carraway[b], Namrata S. Chandhok[c], Thomas Prebet[d]

[a] Roswell Park Comprehensive Cancer Center, Elm and Carlton Streets, Buffalo, NY, USA
[b] Taussig Cancer Institute, Cleveland Clinic, 10900 Euclid Ave, Cleveland, OH, USA
[c] University of Miami, Coral Gables, FL, USA
[d] Smilow Cancer Center at Yale New Haven Hospital, 35 Park Street, New Haven, CT, USA

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ABSTRACT

Acute myeloid leukemia (AML) is primarily a disease of older adults. Many older patients with AML are not candidates for intensive chemotherapy regimens aimed at inducing remission before transplantation. The prognosis for this patient population remains poor, with 5-year overall survival (OS) rates of less than 10 %. At present, there is no standard of care, and clinical trials should be considered. Hypomethylating agents often are the mainstay of treatment in this setting; however, improved genetic profiling and risk stratification based on molecular, biological, and clinical characteristics of AML enhance the ability to identify an individual patient's risk and can refine therapeutic options. Over the past 2 years, several novel agents have been approved for AML patients in either the frontline or relapsed settings. Additional agents have also shown promising activity. It is becoming a challenge for physicians to navigate these different options and select the optimal therapy or combination of therapies. The aim of this review is to summarize the available information to assist with treatment decisions for leukemia patients who are not suitable for intensive chemotherapy.

1. Introduction

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults, with a median age at diagnosis of 68 years [1,2]. The incidence of AML is increasing as the population ages, and management of older patients remains challenging [3,4]. More than 50 % of patients with AML are ineligible for intensive chemotherapy regimens because of age, performance status, and/or comorbid conditions [3,5,6]. Clinical management of this population remains suboptimal given the lack of therapies that are tolerable and offer improved survival and quality of life. Historical data in patients considered ineligible for intensive chemotherapy indicate that survival is approximately 5 months [7]. For these patients, there is no firmly established standard of care. Recently, new agents have been approved in combination strategies for AML patients over age 75 or deemed "unfit for induction." For example, clinicians can now offer venetoclax in combination with either low-dose cytarabine or a hypomethylating agent (based on impressive data, albeit in the phase I/II setting) [8] or glasdegib in combination with low-dose cytarabine, based on more modest response rates in a phase II study [9]. While both of these combinations appear to be superior to single-agent hypomethylating agent therapy, arguably the prior standard of care, most experts would still favor enrollment in a clinical trial for newly diagnosed patients in this category [6]. Elderly patients who are eligible for intensive chemotherapy have higher rates of relapse and lower rates of long-term survival than younger patients; thus, well tolerated, beneficial therapies may be more attractive to them and should be considered part of the comprehensive conversation when deciding on therapy. High-quality studies are urgently needed to identify and standardize effective therapies that improve and sustain quality of life in this elderly patient population.

Hypomethylating agents in combination with targeted agents offer the potential for active therapy alternatives with improved tolerability compared with intensive chemotherapy [8]. Of importance, multidrug resistance, unfavorable karyotypes, and high-risk mutations that predict relative resistance to traditional induction approaches make alternative treatment strategies important even among patients potentially eligible for intensive induction therapy [4,10,11]. The availability of targeted agents has considerable potential benefit for such patients, and molecular profiling tests are becoming more common. Once next-generation sequencing mutation profile results are available, treatment

* Corresponding author at: Roswell Park Comprehensive Cancer Institute, Elm and Carlton Streets, Buffalo, NY, 14263, USA.
E-mail addresses: Elizabeth.Griffiths@RoswellPark.org (E.A. Griffiths), carrawh@ccf.org (H.E. Carraway), nxc691@med.miami.edu (N.S. Chandhok), thomas.prebet@yale.edu (T. Prebet).

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should prioritize actionable mutations and incorporate currently available targeted therapies that have demonstrated clinical benefit. In addition to the treatment challenges, quality of life in these patients has been largely unaddressed and understudied given the challenges of enrolling patients aged 65–70 years and older into clinical trials. Emerging research in hematologic cancers has shown that timely advanced care planning, discussion of goals of care, and early integration of palliative care can improve end-of-life outcomes in this high-risk population [12,13].

This review discusses the approach to selection of best therapies for AML in elderly patients and those who cannot tolerate intensive chemotherapy because of poor performance status or comorbidities in the frontline and relapse settings using a case study format. Key clinical data are reviewed for non-intensive chemotherapy options in adults with AML. In addition, an algorithm is presented to guide treatment and define optimal sequencing based on patient characteristics and cytogenetic and molecular profiling.

2. Treatment options for patients who are not candidates for or who decline frontline intensive chemotherapy

2.1. Case 1

A 74-year-old white man with a medical history notable for mild chronic obstructive pulmonary disease presents to his primary care doctor with worsening dyspnea. The patient reports that he is currently very active, noting that he chopped wood in the forest with his sons last month. A complete blood count reveals a white blood cell count of 110,000/mm^3 with 80 % blasts. The patient is admitted to the hospital and is screened for clinical trial eligibility, including studies of targeted therapies with inhibitors of Fms-like tyrosine kinase 3 (FLT3) and isocitrate dehydrogenase (IDH), or a combination of a hypomethylating agent with a small molecule targeting B-cell leukemia/lymphoma-2 (BCL-2). A bone marrow biopsy confirms a diagnosis of AML with myelodysplastic syndrome (MDS)-related changes. Hydroxyurea is initiated for control of leukocytosis. Molecular profiling is sent and is pending. Preliminary cytogenetic testing demonstrates a normal karyotype. How should this patient be optimally treated, and what are the goals for his care?

2.2. Considerations for frontline therapy

Frontline therapy for AML is intended to reduce leukemic burden [4]. Treatment decisions are influenced by patient- and disease-specific characteristics that determine tolerability and ability to achieve disease control. Important patient-related factors include age, performance status, and comorbid conditions. Characterization of the disease process requires assessment of cytogenetics and molecular abnormalities. Because disease-specific information may not be available before initiation of induction therapy, treatment guidelines employ a standard age cutoff of 60–70 years. Another reason for this classification is that patients aged > 60 years often have unfavorable cytogenetics, multidrug resistance, and comorbid conditions that limit their ability to achieve disease control and/or tolerate intensive chemotherapy regimens.

Age and performance status have been the primary drivers of determining fitness for intensive chemotherapy in AML patients; however, performance status evaluations may be limited in detecting variations in physical function and potentially vulnerable patients within status categories [14]. Geriatric assessment (GA) evaluates multiple patient characteristics, including physical function, comorbid conditions, cognitive function, psychological status, social support, polypharmacy, and nutrition to define fit, vulnerable, and frail patients [14]. In the GA, frail patients have an Eastern Cooperative Oncology Group (ECOG) performance status ≥3, impaired activities of daily living, and major comorbidities; vulnerable patients are those with ECOG performance status < 3 with no major comorbidity, impaired objectively measured physical function, and impaired cognition; fit patients do not have any of these factors. A number of indices that incorporate comorbidities have been developed to help determine fitness and likelihood of positive outcomes with treatment for older AML patients, including the Hematopoietic Stem Cell Transplantation Comorbidity Index (HCT-CI) [15], the Adult Comorbidity Evaluation-27 (ACE-27; available at: https://www.rtog.org/LinkClick.aspx?fileticket=oClaTCMufRA%3D&tabid=290) [16], and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) [17]. In a retrospective analysis of 194 adults with AML, HCT-CI, ACE-27, and CIRS-G were evaluated to determine the impact of comorbidities on OS and to compare these indices in predicting outcomes [18]; this study confirmed the profound effects of comorbidities on OS (although comorbidities did not predict early death), and higher comorbidity on ACE-27 was an independent risk factor for OS, along with poor-risk cytogenetics.

When determining treatment options, enrollment in a clinical trial should systematically be considered as there is no standard of care for patients who are considered unsuitable for induction chemotherapy-based treatment [4]. Current guidelines from the National Comprehensive Cancer Network (NCCN) offer the following treatment considerations for patients who are not candidates for or who decline intensive chemotherapy: hypomethylating agents (5-azacitidine and decitabine) with or without venetoclax, low-dose cytarabine with or without glasdegib or venetoclax, gemtuzumab ozogamicin for CD33-positive patients, enasidenib for isocitrate dehydrogenase (*IDH*)-2-mutated AML, ivosidenib for *IDH1*-mutated AML, hypomethylating agents with sorafenib for *FLT3*-mutated AML, or best supportive care (BSC) with hydroxyurea and transfusion support [4].

Table 1 provides a summary of studies evaluating frontline therapies for this patient population [6–9,19–25]. At minimum, 4 treatment cycles of single-agent hypomethylating agents are required before a response can be evaluated, and these treatments can be continued until progression if the patient tolerates therapy [4].

Following frontline therapy with a hypomethylating agent, assessment of the bone marrow should typically occur at around 4 cycles. If the patient is receiving venetoclax, earlier assessment between 3 and 12 weeks could be considered. It is important not to give up on a therapeutic strategy too early, because some agents can demonstrate a delayed response to treatment: responses can take 3–6 months to manifest and in the absence of overt leukemic progression, continued therapy is advised [4,26]. This is particularly true for single-agent hypomethylating agents and for the differentiation agents targeting IDH. Also, time to best response can be delayed and will unfold only if patients remain on therapy even with stable disease. For patients who achieve response, treatment options include reduced-intensity conditioning (RIC) hematopoietic stem cell transplantation (HCT) or continuation of therapy with low-intensity hypomethylating agents and selected targeted agents until progression (data discussed below).

Allogeneic HCT using RIC is an option for older patients, particularly those who achieve first complete remission (CR) with minimal comorbidities and who have an available donor [4,27,28]. Currently, this approach of debulking the tumor with non-intensive chemotherapy agents followed by RIC allogeneic HCT offers the only curative option for more fragile AML patients [29].

2.3. Hypomethylating agents

Hypomethylating agents are chemical nucleoside analogs that are incorporated directly into DNA (decitabine, azacitidine), irreversibly inhibiting DNA methyltransferase, and into RNA (azacitidine), causing altered protein synthesis and apoptosis of abnormal leukemia cells in the bone marrow [3,5]. These actions reverse the tumorigenic effects of DNA methyltransferase and reactivate silenced tumor suppressor genes [30]. Although the fundamental mechanism for these drugs remains a matter of some debate, the hypothesized contributors to response, including changes in promoter methylation, DNA damage, and alteration

Table 1
Frontline treatment options for patients with AML who are not candidates for or refuse intensive chemotherapy.

Drug	Study	Population	Treatment Arms (n)	Efficacy Outcomes	Safety Outcomes
Azacitidine	AZA-AML-001 [6]	• Newly diagnosed AML • Aged ≥65 y • > 30 % blasts	Azacitidine 75 mg/m^2 x 7 d (n = 241)	mOS: 10.4 mo* 1-y survival: 46.5 % CR/CRi: 27.8 %	30-d mortality: 6.6 %
			Conventional care regimens: • Low-dose cytarabine 20 mg bid x 10 d (n = 158) • BSC (n = 45) • IC (n = 44)	mOS: 6.5 mo 1-y survival: 34.2 % CR/CRi: 25.1 %	30-d mortality: 10.1 %
Azacitidine	AZA-001 [19,20]	• AML with ≥20 % blasts • Aged ≥18 y • No prior azacitidine	Azacitidine 75 mg/m^2 x 7 d (n = 55)	mOS: 24.5 mo* CR: 18 %	Discontinued due to AEs: 7.3 % Hospital admissions per patient: 3.4*
			Conventional care regimens: • Low-dose cytarabine 20 mg bid x 14 d (n = 20) • BSC (n = 27) • IC (n = 11)	mOS: 16.0 mo CR: 16 %	Discontinued due to AEs: 5.2 % Hospital admissions per patient: 4.3
Decitabine	DACO-016 [7]	• Newly diagnosed AML • Aged ≥65 y • Intermediate- or poor-risk cytogenetics	Decitabine 20 mg/m^2 x 5 d (n = 242)	mOS: 7.7 mo* CR/CRi: 17.8 %*	30-d mortality: 9%
			• Low-dose cytarabine 20 mg/m^2 x 10 d (n = 215) • BSC (n = 28)	mOS: 5 mo CR/CRi: 7.8 %	30-d mortality: 8%
Gemtuzumab ozogamicin	EORTC-GIMEMA AML-19 [21]	• Newly diagnosed AML • Aged ≥61y	Gemtuzumab ozogamicin 6 mg/m^2 d1, 3 mg/m^2 d8, followed by 2 mg/m^2 monthly (n = 118)	mOS: 4.9 mo* 1-y survival: 24.3 % CR/CRi: 24.3 %	30-d mortality: 11 %
			BSC (n = 119)	mOS: 3.6 mo 1-y survival: 9.7 %	30-d mortality: 13.5 %
Midostaurin	Cooper et al, 2015 [22]	• Previously untreated AML in elderly (aged ≥70 y) patients • Previously untreated patients of any age who were ineligible for standard induction	Azacitidine 75 mg/m^2/d IV for 7 d then escalating doses of midostaurin (25, 50, and 75 mg bid) d 8-21 q 4 weeks (n = 12)	ORR: 25 % mOS: 6 mo	No dose-limiting toxicity observed; grade 3/4 neutropenia and thrombo-cytopenia observed in most cycles
Ivosidenib	DiNardo et al, 2019 [23]	• Newly diagnosed AML ineligible for intensive treatment	Ivosidenib 500 mg PO continuously + azacitidine 75 mg/m^2/d SC for 7 d q 28 d (n = 23)	ORR: 78 % CR: 57 % CRi/CRp: 13 %	AEs of special interest: QT prolongation (26 %), IDH differentiation syndrome (17 %), and leukocytosis (13 %)
Venetoclax	Wei, et al 2019 [24]	• Previously untreated patients aged ≥60 years ineligible for intensive treatment	Cytarabine 20 mg/m^2 SC d 1-10 + venetoclax 600 mg PO qd (n = 82)	CR/CRi: 54 % CR: 26 % CRi: 28 % mOS: 10.1 mo	30-d mortality: 6 % Most common grade 3/4 AEs were hematologic
Venetoclax	DiNardo, et al 2019 [8]	• Previously untreated patients aged ≥65 y ineligible for intensive treatment	Venetoclax 400, 800, or 1200 mg PO qd with either decitabine 20 mg/m^2 IV, d 1-5, or azacitidine 75 mg/m^2 IV or SC, d 1-7 (n = 145)	ORR: 68 % CR: 37 % CRi: 30 % mOS: 17.5 mo	30-d mortality: 3% Most common grade 3/4 AEs were hematologic
Glasdegib	Cortes, et al 2019 [9,25]	• Newly diagnosed AML • Aged ≥55 y ineligible for intensive treatment	Glasdegib 100 mg PO qd continuously + cytarabine 20 mg/m^2 SC bid for 10 d q 28 d (n = 78)	mOS: 8.3 mo	AEs and serious AEs less frequent in long-term (after > 90 d) vs. short-term (first 90 d)

AE, adverse event; AML: acute myeloid leukemia; bid, twice daily; BSC: best supportive care; CR: complete remission; CRi: complete remission with incomplete recovery of blood counts; d: day; IC: standard intensive induction chemotherapy; IDH, isocitrate dehydrogenase; IV, intravenously; m: month; MDS: myelodysplastic syndrome: mOS, median overall survival; SC, subcutaneously; PO, orally; qd, once daily.
* $P < 0.05$ vs. comparator treatment arm.

of immune signaling, all require cell cycling for their action [31–33].

2.3.1. Azacitidine

A phase III clinical study (AZA-AML-001) compared the efficacy and safety of azacitidine with 3 conventional care regimens (BSC, low-dose cytarabine, or standard induction chemotherapy) in patients aged ≥65 years with newly diagnosed AML and > 30 % bone marrow blasts who were not considered candidates for HCT [6]. Eligible patients had intermediate- or poor-risk cytogenetics, an ECOG performance status of 0–2, and a white blood cell count ≤15 × 10^9/L. A total of 241 patients received azacitidine 75 mg/m^2 for 7 days per 28-day treatment cycle and 247 received conventional regimens. At 24 months' median follow-up, the median OS was 10.4 months with azacitidine and 6.5 months with conventional care (hazard ratio [HR] = 0.85; 95 % confidence interval [CI], 0.69–1.03; P = 0.1009). The estimated 1-year survival rates were 46.5 % in the azacitidine group and 34.2 % in the conventional care group; favorable trends were observed for azacitidine across all subgroups. In particular, the median OS for patients with poor-risk cytogenetics was significantly prolonged with azacitidine (6.4 vs. 3.2 months; HR = 0.68; 95 % CI, 0.50–0.94; P = 0.0185). CR and morphologic CR with incomplete blood count recovery were 27.8 % in the azacitidine group and 25.1 % in the conventional care group. The occurrence and nature of treatment-emergent adverse events (TEAEs) were similar between treatment groups; the most frequent drug-related TEAEs were nausea, neutropenia, and thrombocytopenia.

The Austrian Azacitidine Registry reported an update on the efficacy and safety of azacitidine treatment in 302 patients with AML, including patients with > 30 % bone marrow blasts [34]. The median age was 73 years and patients received a median of 4 treatment cycles. Azacitidine was used as frontline therapy for 46 % of patients, following insufficient response to or early relapse after conventional chemotherapy or allogeneic HCT in 46 %, bridging to allogeneic HCT in 3%, or as maintenance treatment after CR to chemotherapy in 4%. The overall response rate (ORR) was 48 % in the intent-to-treat population and 72 % in patients who received more than 2 cycles of azacitidine. The median time to first response was 3 months, and best response was achieved by cycle 9 in 94 % of responders. The median duration of response was 3.4 months; the median OS was 9.6 months for all patients, and 16.1 months for responders versus 3.7 months for non-responders. Overall, 24 % of all AEs and 20 % of grade 3/4 AEs were attributed to azacitidine. Grade 3/4 hematologic toxicities occurred in 48 % of patients, with neutropenia, thrombocytopenia, and anemia the most frequently reported [34].

2.3.2. Decitabine

Decitabine has been studied in hematologic malignancies across a variety of doses and schedules [5]. A phase III clinical study (DACO-016) evaluated decitabine 20 mg/m^2/day for 5 days (n = 242) versus treatment of choice (supportive care [n = 28] or cytarabine 20 mg/m^2/day for 10 days [n = 215]) in patients aged ≥65 years with newly diagnosed AML and intermediate- or poor-risk cytogenetics [7]. In this high-risk patient population, the median age was 73 years, 24 % had an ECOG performance status of 2, and the median baseline blasts in bone marrow were 46 %. At the time of mature analysis, the median OS was 7.7 months with decitabine and 5.0 months with treatment of choice (HR = 0.82; P = 0.037). In subgroup analyses, the survival advantage was significant for patients aged ≥75 years and for those with *de novo* AML, blasts > 30 %, intermediate cytogenetic risk, or a baseline ECOG performance status of 2. Decitabine was associated with a significantly higher composite CR rate (CR plus CR with incomplete platelet recovery [CRi]) compared with treatment of choice (17.8 % vs. 7.8 %; P = 0.001). The median time to best response was 4.3 months for decitabine and 3.7 months for treatment of choice. The most common grade 3/4 toxicities were thrombocytopenia and anemia, with higher frequencies in patients receiving decitabine (40 % and 34 %, respectively) compared with patients receiving cytarabine (35 % and 27 %, respectively) and supportive care (14 % for each TEAE). Similar 30-day mortality rates were reported in both arms (decitabine: 9%; cytarabine: 8%) [7].

A *post hoc* analysis of the DACO-016 study evaluated the efficacy of decitabine in older patients with AML and higher blast counts (≥30 %) and compared clinical characteristics and outcomes with data from the azacitidine AML-001 study [6,35]. A total of 271 of 485 patients in the DACO-016 study had a high blast count (≥30 %) and white blood cell count < 15 × 10^9/L; median age was 73 years [35]. The CR/CRi rate was 27 % in the decitabine group and 11 % in the treatment-of-choice group. Median OS was significantly prolonged with decitabine versus treatment of choice (8.6 vs. 4.7 months; HR = 0.67; P = 0.0033). The 30-day mortality rate was 10 % in the decitabine group and 6 % in the treatment-of-choice group. Decitabine was associated with higher rates of grade 3/4 hematologic toxicities compared with treatment of choice [35]. These results were generally similar to outcomes reported in the AML-001 study despite the fact that the DACO-016 study did not include intensive chemotherapy as a treatment option, possibly suggesting a more compromised patient population in the latter study [35].

A prospective, uncontrolled study sought to determine if the presence of specific mutations correlated with response to decitabine [36]. Patients with AML who were aged ≥60 years, those with relapsed AML, and those with transfusion-dependent MDS received decitabine 20 mg/m^2/day for 10 days every 4 weeks. Exome and gene-panel sequencing was conducted to detect all common mutations within 8 genes. Of the 116 patients who were treated, the ORR was 46 %, including 15 (13 %) patients who achieved CR. Mutations in *TP53* were highly correlated with response. These mutations were present almost exclusively in patients with unfavorable cytogenetics, and survival was not negatively affected by cytogenetic abnormalities or the presence of *TP53* mutations. Median survival was 11.6 months for patients with unfavorable risk versus 10 months for those with favorable or intermediate risk and 12.7 months for those with *TP53* mutations versus 15.4 months for those with wild-type *TP53* [36].

Use of combination therapy with additional agents (venetoclax) is discussed below; combination strategies, including hypomethylating agents and low-dose cytarabine, were recently approved by the US Food and Drug Administration (FDA) based upon phase 2 data. These regimens can be used in the frontline setting for newly diagnosed patients with AML; the approval language restricts their use to those older than 75 years or with comorbidities that preclude induction. Maturation of the clinical study data is ongoing and will yield further clarity on the risk/benefit ratio of combination-based approaches, particularly with regard to duration of response and real-world toxicity and tolerability profiles. Clear guidelines for management of early and late toxicity with these combinations are limited. Approaches to dose reduction and maintenance are currently based largely upon expert recommendations, which vary widely.

2.4. Targeted therapies currently available for AML

2.4.1. Gemtuzumab ozogamicin

Gemtuzumab ozogamicin, an immunoconjugate consisting of humanized anti-CD33 monoclonal antibody and the DNA intercalator calicheamicin [21], is approved by the FDA for the treatment of adults with newly diagnosed AML whose tumors express the CD33 antigen. This approval comes after withdrawal of the drug from the market due to safety concerns related to early deaths in the relapsed AML population [37].

A phase II/III study compared gemtuzumab ozogamicin with BSC in patients aged ≥61 years with newly diagnosed AML who were unsuitable for intensive chemotherapy. Gemtuzumab ozogamicin was administered as a single induction course of 2 intravenous infusions at doses of 6 mg/m^2 on day 1 and 3 mg/m^2 on day 8. Patients who had CR, partial response, or stable disease could receive up to 8 monthly infusions of gemtuzumab ozogamicin 2 mg/m^2. A total of 237 patients

were enrolled, and the median OS was significantly longer with gemtuzumab ozogamicin versus BSC (4.9 vs. 3.6 months; HR = 0.69; 95 % CI, 0.53–0.90; P = 0.005). The all-cause 30-day mortality was similar between treatment groups (11 % vs. 13.5 %, respectively). Gemtuzumab ozogamicin had a greater effect on survival among patients with > 80 % CD33-positive blasts compared with BSC. The overall CR/CRi rate for induction was 24.3 % for gemtuzumab ozogamicin, and the overall clinical benefit rate (CR/CRi/PR/stable disease lasting > 30 days) was 56.7 %. The median time to best response of CR/CRi was 36.5 days. Mortality related to toxicity occurred in 8 patients and included infection, hemorrhage, renal failure, and cardiac failure. Pancytopenia occurred in all patients receiving gemtuzumab ozogamicin; however, the incidences of nonhematologic AEs and grade 3/4 AEs were similar between treatment groups [21]. Despite a lack of direct comparative studies with other regimens, the available data do not favor using single-agent gemtuzumab ozogamicin as the regimen of choice for a majority of patients.

The triple combination of gemtuzumab ozogamicin, azacitidine, and hydroxyurea was evaluated in a single-arm, open-label, phase II study of patients with newly diagnosed AML [38]. Among good-risk patients (n = 83), CR/CRi was achieved in 44 %; among poor-risk patients (n = 54), CR/CRi was achieved in 35 %. Median OS was 11 months for both risk groups. These results are encouraging but would require confirmation in a larger study. Use of this regimen in good-risk patients who are not eligible for other regimens could be considered but would need to be weighed against the potential for AEs.

The use of sequential gemtuzumab ozogamicin and standard chemotherapy in older patients with newly diagnosed AML was assessed in the phase III EORTC/GIMEMA Consortium AML-17 study [37]. No significant differences in response to induction therapy were observed with the addition of gemtuzumab ozogamicin, and 2 patients died as a result of veno occlusive disease during gemtuzumab ozogamicin therapy. The sequential regimen tested did not benefit older patients with AML and was too toxic for those aged ≥70 years [37].

2.4.2. Midostaurin

Midostaurin is a multi-targeted kinase inhibitor that acts at the *FLT3* receptor in both *FLT3* wild-type and mutant leukemic blasts [22,39]. Preclinical and phase I studies showed synergy between midostaurin and chemotherapy and encouraging efficacy with the use of midostaurin during induction and consolidation chemotherapy [40,41]. Midostaurin is recommended for patients with AML who are eligible to receive intensive chemotherapy and as maintenance therapy for 12 months based on results of the phase III RATIFY study [4,40].

Midostaurin has been assessed in untreated elderly (aged ≥70 years) patients with AML, patients of any age with AML who were not candidates for intensive induction therapy, or patients with relapsed/refractory AML [22]. Patients received azacitidine 75 mg/m^2/day intravenously for 7 days followed by escalating doses of midostaurin (25, 50, and 75 mg twice daily) for days 8–21 every 4 weeks. The median age of the 17 patients enrolled was 73 years, and all patients were *FLT3* negative. No dose-limiting toxicities were observed during midostaurin dose escalation. Grade 3/4 hematologic toxicities were observed in the majority of cycles; during the first 60 days, 2 patients died due to disease progression and 1 patient died of infectious pneumonia and grade 3 hepatotoxicity. Responses were observed in 18 % of all patients and 25 % of patients who were previously untreated. Median survival was 6 months (range, 1–19+ months) for all patients, and results did not differ between previously treated and untreated patients. Since patients on this study were *FLT3* negative, these results cannot be used to inform the efficacy of midostaurin in combination with azacitidine in *FLT3*-mutant elderly AML patients.

2.4.3. Ivosidenib

Ivosidenib (AG-120) is an oral inhibitor of mutant *IDH1* [39], which is approved for the treatment of newly diagnosed patients with *IDH1*-mutant AML who are ≥75 years old or not candidates for intensive chemotherapy, as well as for patients with relapsed/refractory AML [42]. In a phase I dose-escalation study including 179 patients with relapsed/refractory AML and *IDH1* mutation (ECOG performance status 0, 1, 2, and 3 in 20 %, 55 %, 24 %, and 1 % of patients, respectively), ivosidenib 500 mg daily resulted in an ORR of 39.1 % and CR rate of 21.8 % [43]. In patients with newly diagnosed AML who were ineligible for intensive chemotherapy, a phase Ib/II study evaluated ivosidenib 500 mg/day in combination with azacitidine 75 mg/m^2/day for 7 days every 4 weeks in those with *IDH1*-mutant disease [23,44]. In a preliminary report, which included 23 patients (median age 76 years; median treatment duration 11 months [range, 0.3–25.3]), there were 18 responses to combination therapy (78 %), of which 16 (70 %) were CR or CR with partial hematologic recovery. The phase III AGILE study has been initiated to assess the efficacy and safety of ivosidenib and azacitidine in untreated adult patients with AML who are considered appropriate candidates for non-intensive chemotherapy (NCT03173248). A boxed warning is included in the ivosidenib prescribing information for IDH inhibitor–associated differentiation syndrome, which is potentially life-threatening and caused by rapid differentiation and proliferation of myeloid cells [42]. Symptoms of differentiation syndrome include non-infectious leukocytosis, peripheral edema, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonitis, pericardial effusion, rash, fluid overload, tumor lysis syndrome, and increased creatinine. Differentiation syndrome was observed with ivosidenib in 25 % (7/28) patients with newly diagnosed AML and 19 % (34/179) patients with relapsed/refractory AML. For suspected differentiation syndrome, dexamethasone 10 mg intravenously (or equivalent) every 12 h for a minimum of 3 days is recommended along with hemodynamic monitoring. For non-infectious leukocytosis, hydroxyurea or leukapheresis is recommended as clinically indicated. Treatment with ivosidenib should be interrupted if symptoms persist for more than 48 h.

2.4.4. Venetoclax

BCL-2 is an anti-apoptotic protein with increased expression in AML blasts, which has been associated with AML cell survival and chemotherapy resistance [45–47]. Venetoclax is a BCL-2 inhibitor that has been evaluated in patients with relapsed/refractory AML and those with untreated AML who were not candidates for intensive chemotherapy in 2 early phase studies; ECOG performance status was 0 in 3 patients (9 %), 1 in 14 patients (44 %), and 2 in 14 patients (44 %) [46,48]. In a phase II, single-arm study of venetoclax monotherapy (800 mg/day), 6 of 32 (19 %) patients achieved CR/CRi. Among 12 patients with *IDH1/2* mutations, the rate of CR/CRi was 33 %. Venetoclax (600 mg/day) was used in combination with low-dose cytarabine (20 mg/m^2 daily for 10 days every 4 weeks) in a phase Ib/II study in 82 patients ≥60 years of age with AML who were not suitable for intensive chemotherapy; ECOG performance status was 0 in 12 patients (15 %), 1 in 46 patients (56 %), 2 in 23 patients (28 %), and 3 in 1 patient (1 %) [48]. The CR/CRi rate was 54 %, and median OS was 10.1 months. The most common grade 3/4 AEs were hematologic; serious AEs in ≥5 % of patients were anemia (31 %), febrile neutropenia (27 %), pneumonia (10 %), and sepsis (7 %).

Venetoclax also has shown synergy with hypomethylating agents in preclinical models and is currently being evaluated in combination with azacitidine or decitabine in elderly patients (aged ≥65 years) with previously untreated AML who were ineligible for intensive chemotherapy [8,45]. A total of 145 patients (median age 74 years) were enrolled; ECOG performance status was 0 in 32 patients (22 %), 1 in 90 patients (62 %), and 2 in 23 patients (16 %). Final doses of venetoclax in the expansion phase of this study were 400 (n = 60), 800 (n = 74), or 1200 mg (n = 11). At a median follow-up of 15.1 months in all patients (n = 145), the ORR (CR + CRi + PR) was 68 %, including CR in 37 % and CRi in 30 %, and the median OS was 17.5 months. In the venetoclax 400-mg/hypomethylating agent treatment group, the CR +

CRi rate was 73 %, with median survival not reached. Among evaluable patients with *FLT3* mutations (n = 18), *IDH1* or *IDH2* mutations (n = 35), *NPM1* mutations (n = 23), or *TP53* mutations (n = 36), the CR/CRi rates were 72 %, 71 %, 91 %, and 47 %, respectively. The most common grade 3/4 AEs were febrile neutropenia (43 %), decreased white blood cell count (31 %), anemia (25 %), thrombocytopenia (24 %), neutropenia (17 %), and pneumonia (13 %). These data suggest response rates comparable to those achieved with induction chemotherapy, raising the possibility of a new standard of care, although larger studies are needed for confirmation [49]. Based on the encouraging efficacy and manageable toxicity observed with venetoclax 400 mg in combination with hypomethylating agents, an ongoing phase III trial is currently evaluating venetoclax 400 mg plus azacitidine in patients with untreated AML who are not eligible for intensive induction therapy [8]. Activity appears to be suboptimal when used in the relapsed/refractory setting [50]. Doses of venetoclax should be reduced when administered with posaconazole (to a maximum of 70 mg) or other strong CYP3A inhibitors (to a maximum of 100 mg) [51]. Although the median age in this study was 74 years, it is critical to note that more than 60 % of those enrolled had excellent performance status (ECOG 0–1), raising the question of tolerability in the broader context of elderly patients with AML. The authors of this article have observed substantial rates of toxicity with this regimen in patients who do not meet this performance status standard. Many patients are not eligible for treatment with venetoclax-based regimens because of poor performance status. We have found that if patients with poor performance status are treated with venetoclax-based combinations, mortality can be uncomfortably high.

The vast majority of patients will be cytopenic at the end of cycle 1 of the combination of venetoclax and hypomethylating agents. For these patients, the general consensus is to evaluate the bone marrow status during the fourth week of cycle 1 and to hold venetoclax for patients without evidence of active disease until count recovery or day 42. For patients with count recovery or persistent disease on the marrow evaluation, the treatment course is maintained and cycle 2 is given on schedule, starting cycle 2 on day 29 of cycle 1. It may be necessary to decrease the duration of venetoclax treatment (and/or discontinue) in subsequent cycles if prolonged cytopenias persist and bone marrow has demonstrated CR/CRi.

Venetoclax is not always accessible to all patients, as there may be copay cost and insurance approval issues, as well as concerns for toxicity in older patients with prolonged aplasia and in patients with poor performance status. Because many patients may not have access to this combination, some physicians are waiting to use this combination until a clear survival benefit is demonstrated. An overview of standard practices when administering venetoclax plus hypomethylating agents to patients with newly diagnosed AML was recently published to help guide clinicians. [52]

2.4.5. Glasdegib

Glasdegib (PF-04449913), an oral, small-molecule inhibitor of the Hedgehog pathway component Smoothened [53], is approved in combination with low-dose cytarabine for newly diagnosed AML in patients ≥75 years of age or who are not eligible for intensive chemotherapy [54]. In a randomized, phase II study in patients ≥55 years of age with untreated AML or high-risk MDS, patients received either glasdegib 100 mg orally daily in 28-day cycles in combination with low-dose cytarabine or low-dose cytarabine alone until disease progression, unacceptable toxicity, or patient refusal [9,25]. At a median follow-up of approximately 43 months, glasdegib plus low-dose cytarabine (n = 78) resulted in significantly longer OS compared with low-dose cytarabine alone (n = 38; 8.3 months vs. 4.3 months, respectively; $P = 0.0004$). The most common grade 3/4 nonhematologic AEs observed with glasdegib/low-dose cytarabine (safety population, n = 88) were pneumonia (17 %), fatigue (14 %), dyspnea (7 %), hyponatremia (6 %), sepsis (6 %), and syncope (6 %).

2.5. Post-remission therapy

In patients with AML, post-remission therapy (e.g., consolidation and maintenance therapy) can potentially maintain and/or prolong remission by eliminating residual leukemic cells and preventing relapse [4]. Typically, low-risk AML patients receive successive cycles of chemotherapy alone, and higher-risk patients undergo HCT. Generally, post-remission therapy is individualized based on risk, specific genetic alterations, and patient factors (e.g., performance status) [4,10]. Medeiros and colleagues recently reviewed key data evaluating post-remission therapies in patients with AML [55].

The value of azacitidine treatment in the post-remission setting was evaluated in a phase III randomized study (HOVON97) [56]. A total of 116 patients with AML who achieved CR/CRi after 2 cycles of intensive induction chemotherapy were randomized to azacitidine 50 mg/m^2/day for 5 days every 4 weeks for 12 cycles, or observation. The 12-month disease-free survival (DFS) rate was significantly higher in the azacitidine group than in the observation group (64 % vs. 42 %; $P = 0.04$).

Results were recently reported from a phase III, randomized study (QUAZAR) of oral azacitidine (CC-486) as maintenance therapy in patients with newly diagnosed AML who had achieved first complete response or complete response with incomplete blood count recovery [57]. A total of 472 patients were enrolled, 238 randomized to CC-486 and 234 randomized to placebo, with a median age of 68 years (range: 55–86); 91 % of patients had de novo AML. Following induction therapy, 81 % of patients achieved a complete response and 19 % of patients achieved a complete response with incomplete count recovery; 80 % of patients received consolidation chemotherapy. At a median follow-up duration of 41.2 months, maintenance CC-486 resulted in significant improvement in OS versus placebo (24.7 vs. 14.8 months, respectively; $P = 0.0009$) [58] and relapse-free survival (10.2 vs. 4.8 months; respectively; $P = 0.0001$). Both OS and relapse-free survival improvements with CC-486 were observed regardless of cytogenetic risk status, number of prior consolidation cycles, and complete response/complete response with incomplete status. CC-486 had a safety profile similar to that of intravenous azacitidine. CC-486 is the first maintenance therapy showing a significant improvement in overall and relapse-free survival.

2.6. Case 1 continued

The patient elects to participate in a clinical trial combining decitabine and venetoclax for management of newly diagnosed AML. He begins therapy with the combination (decitabine 20 mg/m^2 IV over 1 h for 5 days with venetoclax 100, 200, and 400 mg over days 1, 2, and 3, respectively, and 400 mg thereafter). A week later, mutational profiling reveals an atypical *FLT3* tyrosine kinase domain (TKD) mutation as well as a mutation in *IDH1*. The venetoclax dose is reduced to 100 mg due to the use of concomitant posaconazole, a strong cytochrome P450 3A inhibitor, for fungal prophylaxis [59]. Table 2 shows the recommended dose adjustments for venetoclax when coadministered with posaconazole [51]. After 2 cycles of therapy, the patient achieves a CR. He does well for 15 months, requiring alterations in the dosing of venetoclax and decitabine due to intermittent cytopenias. He is transfusion independent and has excellent quality of life. Unfortunately, at a follow-up visit he is noted to have new cytopenias and requires a platelet transfusion for the first time in months. A repeat bone marrow biopsy with molecular profile is performed. This demonstrates reoccurrence of the *IDH1* mutation and expansion of the variant allele frequency (VAF) for his atypical *FLT3* mutation. After discussion with his doctor, he elects to start oral therapy with an IDH1 inhibitor. He achieves a partial remission from this, but ultimately dies of refractory leukemia. This case highlights a frequent experience in the management of elderly patients in which brief periods of response are followed by swift disease progression with loss of quality of life.

Table 2
Recommended venetoclax dose adjustments when coadministered with CYP3A and P-gp inhibitors in patients with AML [51].

Coadministered Drug	Initiation and Ramp-Up Phase		Steady Daily Dose
	Day	Dose	
Posaconazole	1	10 mg	70 mg
	2	20 mg	
	3	50 mg	
	4	70 mg	
Other strong CYP3A inhibitor	1	10 mg	100 mg
	2	20 mg	
	3	50 mg	
	4	100 mg	
Moderate CYP3A inhibitor P-gp inhibitor	Reduce venetoclax dose by at least 50 %		

CYP3A, cytochrome P450 3A; P-gp, P-glycoprotein.

2.7. Treatment algorithm

Fig. 1 shows a treatment algorithm focusing on patients with AML who are not candidates for or refuse intensive chemotherapy. Considerations are given for patient and disease characteristics, including cytogenetics, molecular classification, comorbidities, and functional, social, and cognitive status of the patient [4,27]. Favorable cytogenetics and mutations, such as core binding factor leukemia or mutated *NPM1*, may encourage use of more intensive therapy; whereas unfavorable *FLT3* gene mutations may suggest use of a targeted agent in conjunction with a hypomethylating agent. Similarly, if patients are known to be CD33-positive or have a mutation in *IDH*, targeted treatment options are available. It is important to consider the mutational background when selecting a truly targeted therapy such as an IDH inhibitor because concurrent mutations involving the *RAS* pathway may reduce the effectiveness of single-agent IDH inhibitors. The assessment of clinical

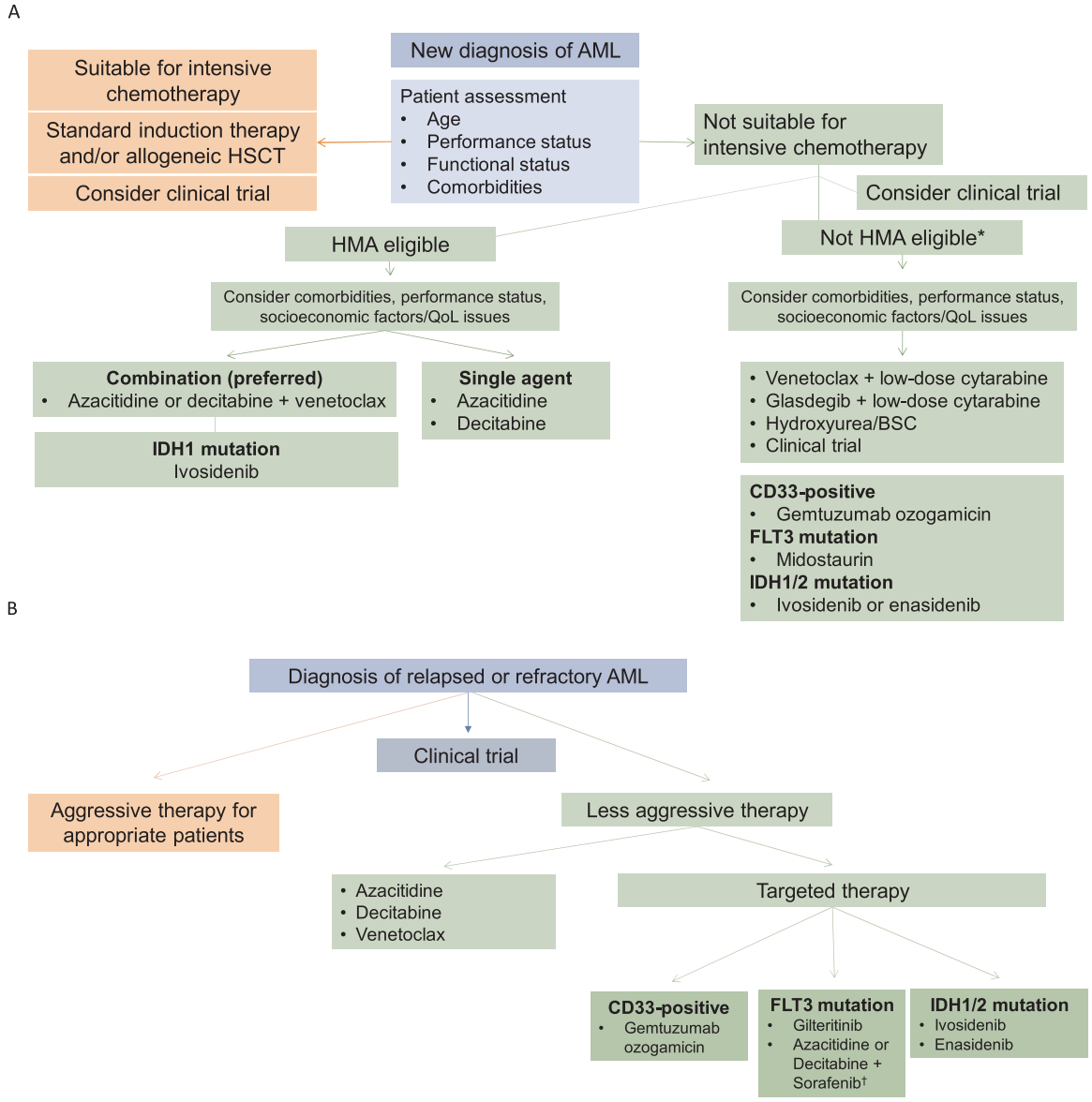

Fig. 1. Treatment algorithm, focusing on patients who are not suitable candidates for intensive chemotherapy in (A) newly diagnosed AML and in (B) relapsed/refractory AML.
*Defined as patients with poor performance status, comorbidities that preclude any chemotherapy/toxic agent, or lack of a support mechanism (social support) to travel to the clinic 1–2 times a week for laboratory assessments and transfusion support.
†Not approved for AML.
AML: acute myeloid leukemia; BSC: best supportive care; FLT3: Fms-like tyrosine kinase 3; IDH: isocitrate dehydrogenase.

performance status and medical comorbidities is among the most important variables to consider when evaluating a patient's ability to tolerate treatment. Although combinations of hypomethylating agents with venetoclax have demonstrated remarkable rates of upfront response and as a result are approved in "unfit" AML patients and those ≥75 years of age, the majority of those enrolled on trial had a performance status of < 2. Patients develop profound cytopenias, and the rates of sepsis and neutropenic fever are high, leading some experts to mandate hospital admission during the first course of such therapy.

3. Treatment options for patients with relapsed or refractory AML who are not candidates for or who decline intensive chemotherapy

3.1. Case 2

A 79-year-old white man previously in excellent medical health presents for medical attention after pushing a classic car uphill. His friends had called 911 when he developed substantial shortness of breath during the car breakdown. In the emergency room, his white blood cell count is 250,000/mm^3 with monocytosis and circulating blasts. After he is transferred to the cancer center, bone marrow biopsy confirms monocytic AML associated with a complex karyotype. The patient receives induction chemotherapy with 7 + 3 and, at the time of hospital discharge, is wheelchair bound with bilateral pitting edema to the knees. His complete blood count is notable for persistent thrombocytopenia, with a platelet count of 90,000/mm^3. Bone marrow aspirate and biopsy show persistent cytogenetic abnormalities with 15 % blasts. The patient is no longer a candidate for intensive therapy due to his poor performance status.

Molecular profiling of his diagnostic sample reveals mutations in *TET2* (VAF of 0.5) and a *FLT3*-ITD mutation with VAF of 0.8. He consents to initiation of azacitidine 75 mg/m^2 subcutaneously 7 days out of a 28-day cycle with sorafenib 400 mg orally BID [4,60]. Once at home, his performance status markedly improves and he returns to his previous baseline, living independently, working about the house, and feeling strong. Repeat bone marrow biopsy after 4 months on azacitidine/sorafenib demonstrates blast clearance and normalization of peripheral blood counts consistent with CR.

3.2. Considerations in selecting therapies for relapsed or refractory AML

If a patient fails to achieve a response or has disease progression and chooses to receive treatment after relapse, several options exist. Enrollment in a clinical trial is preferred for early (< 12 months) and late relapses. Chemotherapy followed by RIC allogeneic HCT offers another option regardless of the timing of relapse; however, it is important that the patient achieve remission before transplant. Re-treatment with successful initial frontline therapy is an option for late (≥12 months) relapses. Treatment based on molecular mutations offers targeted therapy options for relapsed patients.

3.3. Regimens with activity in relapsed or refractory AML

3.3.1. Novel agents with activity in relapsed or refractory AML

3.3.1.1. Enasidenib. Enasidenib is an oral, selective, small-molecule inhibitor of mutant IDH2 enzymes. A phase I/II study of enasidenib was conducted in adults with advanced *IDH2*-mutant myeloid malignancies and included an expansion cohort of patients with relapsed/refractory AML (n = 176; 74 % of all patients). The median age of patients with relapsed/refractory AML in this study was 67 years, and ECOG performance status was 0, 1, and 2 in 22 %, 60 %, and 18 % of patients, respectively. The ORR for this population was 40.3 %, with 19.3 % achieving CR. The median time to first response was 1.9 months. Median OS was 19.7 months for patients with CR and 14.4 months for those with PR, and the median OS was 9.3 months. The most common drug-related AEs were an elevation of total bilirubin (38 %) and nausea (23 %). Grade 3/4 IDH-associated differentiation syndrome (i.e., retinoic acid syndrome) occurred in 6 % of patients. The results of this study led to the approval of enasidenib for the treatment of adult patients with relapsed/refractory AML and an *IDH2* mutation. An analysis of samples from relapsed/refractory AML patients showed that enasidenib inhibited both R140 and R172 *IDH2*-mutated disease, and response was not dependent on VAF. Patients with higher mutational burden or mutation in the *RAS* pathway were noted to be less likely to respond to enasidenib.

The approval of enasidenib by the FDA was based on phase II data. A phase III, multicenter, randomized study evaluating enasidenib versus conventional care regimens (IDHENTIFY; NCT02577406) is ongoing in patients aged ≥60 years who have relapsed or are refractory to second- or third-line therapy for AML (intensive chemotherapy, low-dose cytarabine, azacitidine, or decitabine).

Like ivosidenib, enasidenib product labeling carries a boxed warning for differentiation syndrome [61]. Further analysis by a differentiation syndrome review committee showed probable or possible cases of IDH-associated differentiation syndrome occurred in 12 % of patients (n = 33) in the phase 1/2 study [62]. Most patients (85 %) were managed with corticosteroid therapy for a median of 12 days (range: 4–43). Enasidenib dosing was interrupted in 15 patients (46 %); 2 patients received reduced enasidenib doses, but none discontinued treatment permanently because of differentiation syndrome.

3.3.1.2. Gilteritinib. Gilteritinib (ASP2215) is a selective FLT3/AXL inhibitor with activity against *FLT3*-ITD and *FLT3*-TKD mutations [63]. This agent was tested in a phase I/II, international, open-label study. A total of 252 patients with relapsed or refractory AML were enrolled; 162 patients in this study harbored *FLT3*-ITD mutations [64]. The OR rate was higher among those with *FLT3* mutations (49 %) compared to those with wild-type *FLT3* (12 %). *FLT3*-positive patients who received ≥80 mg of gilteritinib achieved an OR rate of 52 % and median survival of 31 weeks. In a phase III study (ADMIRAL) comparing gilteritinib with salvage chemotherapy in *FLT3*-mutant patients with relapsed/refractory AML (N = 371; NCT02421939), gilteritinib resulted in higher CR/CR with full or partial hematologic recovery rates (34 % vs. 15 %) and significantly improved median OS (9.3 vs. 5.6 months; $P < 0.001$) compared with standard chemotherapy [65]. These improvements were observed irrespective of comutations, including patients with *NPM1*, *DNMT3A*, *DNMT3A/NPM1*, or wild-type-1 comutation positive or high *FLT3* allelic ratio [66]. Among patients with *FLT3*-TDK mutations alone, CR rates observed with gilteritinib were similar to those in patients with *FLT3*-IDK mutations alone (19.0 % and 20.5 %, respectively) and were similar to CR rates in the overall population (21.1 %). Gilteritinib is now approved as a single agent in the United States and Japan for use in patients with relapsed/refractory AML with *FLT3* mutations.

3.3.1.3. Quizartinib. Quizartinib is a highly selective FLT3 inhibitor [39]. A phase I study in patients with relapsed/refractory AML or who were unsuitable for intensive chemotherapy (n = 76) showed an ORR of 30 % [67]. For 17 patients with *FLT3*-ITD mutations, the response rate was 53 %. Grade 3/4 AEs related to quizartinib included prolonged QT interval, anemia, fatigue, thrombocytopenia, and hypoalbuminemia. Quizartinib also has been tested in combination with azacitidine or low-dose cytarabine in high-risk MDS, chronic myelomonocytic leukemia, or AML in a phase I/II study [68]. Of 59 evaluable patients, the ORR was 73 %, with 76 % responding in the azacitidine arm and 67 % responding in the low-dose cytarabine arm. The median OS was 20 months for all patients, 13.4 months with azacitidine plus quizartinib, and 6.7 months with cytarabine plus quizartinib. These findings led to the initiation of the QUANTUM-R phase III study of quizartinib monotherapy compared with salvage chemotherapy in patients with relapsed/refractory AML and *FLT3*-ITD mutation (NCT02039726). A total of 367 patients were randomized to

quizartinib (n = 245) or investigator's choice of standard therapy (n = 122) [69]. At a median follow-up of 102.4 weeks, median OS was 6.2 months in the quizartinib group versus 4.7 months in the standard therapy group (OS HR = 0.76 [95 % CI: 0.58–0.98]; P = 0.02), with estimated 1-year survival probabilities of 27 % and 20 %, respectively. The safety profile observed with quizartinib was similar to that observed in prior studies at similar doses. Despite the positive results of this trial, the FDA did not approve quizartinib monotherapy for patients with relapsed/refractory AML. These data highlight the superiority, in terms of both efficacy and toxicity, of a targeted oral therapy over more conventional cytotoxic approaches in the context of relapsed/refractory *FLT3*-ITD-mutant AML.

3.3.2. Combination regimens with activity in relapsed/refractory AML

A variety of combination regimens have shown clinical activity in patients with AML and may be feasible options for elderly patients or patients who are not candidates for intensive chemotherapy [60,70]. Specifically, the combination of sorafenib, a multikinase inhibitor with activity against AML cells with *FLT3*-ITD, with other agents may improve efficacy due to the rapid development of resistance to single-agent sorafenib [71].

3.3.2.1. Azacitidine plus sorafenib. The efficacy and safety of combination therapy with azacitidine 75 mg/m^2/day once daily for 7 days and continuous sorafenib 400 mg twice daily were evaluated in a single-arm, phase I/II study [60]. Patients with AML were eligible if they had failed prior induction therapy or relapsed after achieving response to prior therapy. Also eligible were patients aged > 60 years who refused or were not candidates for standard induction therapy. A total of 43 patients were enrolled; median age was 64 years. The ORR was 46 %, with 16 % achieving CR, 27 % achieving CRi, and 3% achieving PR. These responses were achieved at a median of 2 months and lasted for a median of 2.3 months. The median OS was 6.2 months and significantly longer for responders (7.8 months) compared with non-responders (6 months; P = 0.01). The most common grade 3 or higher AEs were thrombocytopenia, neutropenia, anemia, and neutropenia with fever or infection. This study also evaluated the concentration of FLT3 ligand and its association with response. Treatment with low-intensity azacitidine plus continuous sorafenib had minimal to no effect on plasma FLT3 concentrations, and *in vivo* FLT3 inhibition was highly variable. Sorafenib concentrations were correlated with FLT3 inhibition, and patients who achieved > 15 % FLT3 inhibition had a longer median survival (238 days) than patients who did not reach this level of inhibition (154 days).

3.3.2.2. Decitabine plus sorafenib. Preclinical and clinical experience with the combination of decitabine and sorafenib was reported by Muppidi et al. [71]. Decitabine and sorafenib exhibited synergy in the *FLT3*-mutant human MV4-11 AML cell line. Of 6 patients with confirmed *FLT3*-ITD-mutant AML who received decitabine (20 mg/m^2/day) and sorafenib (200 or 400 mg twice daily), 5 attained response, including 1 CR and 4 CRi. The median OS was 155 days, and the most common complication was neutropenic infections. These results warrant further study and may offer an option for older patients with FLT3-mutant AML who are not suitable for intensive chemotherapy.

3.3.2.3. Azacitidine or decitabine plus midostaurin. A single-arm study was performed evaluating azacitidine plus midostaurin in adults with MDS or AML who were not suitable for or refused intensive chemotherapy or had relapsed/refractory AML [72]. A total of 54 adults were enrolled in the study and 74 % harbored an *FLT3* mutation on the AML. The ORR was 26 %. In patients with *FLT3* mutation and no prior exposure to FLT3 inhibitors, the response rate was 33 % and the duration of response was significantly longer than in patients previously exposed to FLT3 inhibitors (31 vs. 16 weeks; P = 0.05). The median OS was 22 weeks, and hematologic toxicities were the most common AEs.

An open-label, phase I, dose-escalation study determined the feasibility of decitabine plus midostaurin in adults with relapsed/refractory AML or patients aged ≥60 years with previously untreated AML who were not eligible for standard induction therapy [73]. Fifteen patients were treated, and 4 patients achieved CR/CRi. Clinical response was negatively associated with baseline white blood cell count, with lower response rates observed with higher white blood cell counts (r = −0.67; P = 0.02). The median duration of response was 107 days, and the most frequent grade 3/4 AEs were neutropenia/granulocytopenia (94 %) and thrombocytopenia (50 %).

Phase II studies of both combinations, azacitidine plus midostaurin (NCT01093573) and decitabine plus midostaurin (NCT01846624, NCT02634827), have been initiated in elderly patients with newly diagnosed AML [39]. To be eligible for the decitabine plus midostaurin studies, a patient's AML must have an *FLT3* mutation.

3.4. Emerging therapies for patients with AML who are not suitable for intensive chemotherapy

Guadecitabine is currently available only to patients participating in a clinical trial. A subcutaneously administered hypomethylating agent may improve tolerability and quality of life over currently available hypomethylating agents for older patients.

3.4.1. Guadecitabine (SGI-110)

Guadecitabine is a next-generation hypomethylating agent that links decitabine and deoxyguanosine by a phosphodiester bond, providing a prolonged half-life and exposure in leukemia cells [74]. A phase I study in heavily pretreated patients with relapsed/refractory MDS (n = 19) or AML (n = 74) showed clinical activity [75]. Subsequently, a phase I/II, multicenter, randomized, open-label study of guadecitabine was conducted in treatment-naive patients aged ≥65 years with AML who were not candidates for intensive chemotherapy [74]. Patients were randomized to receive guadecitabine 60 mg/m^2 or 90 mg/m^2 subcutaneously on days 1–5 of 28-day cycles or guadecitabine 60 mg/m^2 on days 1–5 and 8–12 of 28-day cycles for at least 2 cycles before reducing to the 5-day treatment cycle. Of 107 patients enrolled (median age, 77 years), 54 received the 5-day schedule and 53 received the 10-day schedule. Although the 10-day schedule resulted in deeper and longer DNA demethylation compared with the 5-day schedule, there were no differences in response between the dosing schedules. Composite CR (CR, CR with incomplete platelet recovery, or CR with incomplete neutrophil recovery regardless of platelets) was achieved by 54 % of patients receiving 60 mg/m^2 for 5 days, 59 % receiving 90 mg/m^2 for 5 days, and 50 % receiving 60 mg/m^2 for 10 days. OS was significantly prolonged in patients who achieved composite CR versus those with no response (574 vs. 93 days; P < 0.0001). The most common grade 3 or higher AEs were febrile neutropenia, thrombocytopenia, neutropenia, pneumonia, anemia, and sepsis. More patients died because of AEs in the 10-day treatment group (27 %) versus the 5-day group (18 %), and 4 of these deaths were considered treatment related, all of which occurred in the 10-day group. Recent results of a phase III study of guadecitabine 60 mg/m^2 in a 5-day schedule in patients with AML who are not candidates for intensive chemotherapy (NCT02348489) indicated that the co-primary endpoints (complete response rate and OS) were not met; analysis of secondary endpoints is ongoing [76].

3.4.2. Crenolanib

Crenolanib is a selective pan-FLT3 inhibitor of ITD and TKD mutants, such as *FLT3/D835*, which may present as sorafenib or quizartinib resistance [77]. In an open-label, single-center, phase II study, 38 patients with relapsed/refractory AML and *FLT3*-ITD or *FLT3*-TKD mutations received crenolanib [78]. In this heavily pretreated

population with a median of 3.5 prior therapies, the ORR was 47 %, and 12 % of patients had CRi. The median OS was significantly longer in FLT3 inhibitor-naive patients compared with those patients previously treated with FLT3 inhibitors (55 weeks vs. 13 weeks; $P = 0.03$).

Two phase II studies of crenolanib are ongoing, one in patients with newly diagnosed AML with *FLT3* mutations who are receiving standard induction and consolidation therapy [79] and the other in patients with multiply relapsed or refractory AML who are receiving salvage idarubicin and high-dose cytarabine followed by crenolanib [80]. In interim analyses, CR/CRi rates were 96 % (24/25 evaluable) in newly diagnosed patients and 67 % (4/6 evaluable) in relapsed or refractory patients who received no more than 2 prior therapies. Currently, there are no studies of crenolanib in patients who are not candidates for intensive chemotherapy. Crenolanib is currently accessible only through a clinical trial, but it may receive marketing approval soon. However, its thrice-daily regimen may limit its acceptance among elderly patients with comorbidities receiving multiple medications.

3.5. Case 2 continued

The patient does well for 2 years, but unfortunately develops disease relapse. Repeat molecular profiling reveals a *FLT3*-TKD mutation. He is not interested in any form of intensive therapy but consents to receive treatment on an expanded access protocol for patients with *FLT3* mutations. Following 2 months of therapy, he has stable disease without an increase in blasts and he requires transfusion support every 2 weeks. He reports that he is satisfied with his current quality of life and recognizes that this is not a curative strategy. A conversation about end of life is opened and he elects to be designated Do Not Resuscitate/Do Not Intubate. Three months later, he dies at home in hospice care after developing pneumonia for which he had declined admission to the hospital.

3.6. Other IDH inhibitors

FT-2102, an oral inhibitor of mutant IDH1, is being investigated as a single agent and in combination with azacitidine for relapsed/refractory AML with a documented *IDH1-R132* mutation (NCT02719574) [39]. Other IDH1 inhibitors include IDH-305, BAY19036, and the pan IDH1/IDH2 inhibitor, AG-881.

Mutations of *IDH1/2* are found in approximately 20 % of patients with AML [81]. These mutations cause increased levels of DNA damage in primary AML cells, which suggests potential use in combination with DNA repair inhibitors, such as poly(ADP-ribose) polymerase (PARP) inhibitors [82,83]. Treatment with a PARP inhibitor had an additive effect on the killing of IDH1/2-mutated AML cells, providing rationale for further study in clinical trials. The use of this combination outside a clinical trial is not currently recommended.

3.6.1. CD3xCD123 dual-affinity retargeting protein

Dual-affinity retargeting (DART) proteins are bispecific antibodies that combine 2 peptides with 2 antigen recognition sites [84]. A CD3xCD123 DART (MGD006; flotetuzumab) has been developed for AML [84,85]. In preclinical studies, MGD006 induces T-cell activation and expansion, which leads to killing of CD123-expressing leukemia cells. It was designed to have greater affinity for CD123 than CD3 and depletes circulating levels of CD123-postiive cells at low doses [85]. Cytokine release occurred in MGD006-treated animals as a first-dose phenomenon that was manageable with repeated or escalating doses. A phase I study of MGD006 in patients with relapsed/refractory AML or MDS not expected to benefit from intensive chemotherapy is underway (NCT02152956). Preliminary results of this study were reported at the American Society of Hematology (ASH) annual meeting in 2017 [86]. Forty-five patients with relapsed or refractory AML or MDS of median age 64 years (range, 29–84 years) were treated. Toxicities were largely related to immune activation and included cytokine release and infusion reactions (76 % of treated patients). Fourteen patients were evaluable for response; antileukemic activity was observed in 6 patients by IWG criteria (3 CR, 1 CRi, 1 PR, 1 morphologic leukemia-free state). Responses were seen within 1 cycle of therapy. Combination studies with this agent are under development and remain an option in the context of a clinical trial for elderly patients to consider.

4. Conclusions

Selecting optimal therapies for patients with AML who are ineligible for intensive chemotherapy represents a significant treatment challenge. The availability of non-chemotherapy options has expanded in recent years; however, continued research is necessary to help define the most effective and tolerable regimens and identify the most effective therapeutic sequence based on patient and disease factors. In addition, treatment decisions must consider individual patients' goals, time to response, treatment toxicity, and convenience for patients. The presence and interaction of various gene mutations challenge the ability of clinicians to determine the clinical benefit of targeted therapies. Clinical trials continue to evaluate combination regimens incorporating targeted agents and their ability to overcome resistance associated with single-agent therapy [27,39]. In addition to the investigation of new and more tolerable regimens for this high-risk older population, attention should be directed toward improving their quality of life via timely discussions of goals of care and personal expectations and early integration of palliative care services.

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Author contributions

All authors: Substantial contributions to or interpretation of the design of the work

All authors: Drafting the work or revising it critically for important intellectual content

All authors: Final approval of the version to be published

All authors: Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of Competing Interest

EAG Alexion Pharmaceuticals, AbbVie Inc, Celgene Corporation, Genentech Inc., Novartis Pharmaceuticals, Otsuka/Astex Pharmaceuticals, Boston Biomedical, Onconova Therapeutics (honoraria, advisory board, clinical trial investigator, and/or research funding).

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