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REVIEW ARTICLE

Management of Relapsed/Refractory Acute Myeloid Leukemia in the Elderly: Current Strategies and Developments

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Abstract Elderly patients with acute myeloid leukemia (AML) who are refractory to or relapse following frontline treatment constitute a poor-risk group with a poor long-term outcome. Host-related factors and unfavorable disease-related features contribute to early treatment failures following frontline therapy, thus making attainment of remission and long-term survival with salvage therapy particularly challenging for elderly patients. Currently, no optimal salvage strategy exists for responding patients, and allogeneic hematopoietic stem cell transplant is the only curative option in this setting; however, the vast majority of elderly patients are not candidates for this procedure due to poor functional status secondary to age and age-related comorbidities. Furthermore, the lack of effective salvage programs available for elderly patients with recurrent AML underscores the need for therapies that consistently yield durable remissions or durable control of their disease. The purpose of this review was to highlight the currently available strategies, as well as future strategies under development, for treating older patients with recurrent AML.

Key Points

Older patients with relapsed and refractory acute myeloid leukemia (AML) constitute a poor-risk group who are particularly vulnerable to treatment-related toxicities, and responses to salvage therapies remain poor.

Treatment options for the majority of older patients with relapsed and refractory AML are largely limited to low-intensity strategies that aim to reduce treatment-related mortality and provide disease control.

At the present time, there is no consensus as to how to manage this poor-risk group outside a clinical trial.

1 Introduction

Acute myeloid leukemia (AML) is most often encountered in the elderly (commonly defined as individuals older than 60 years of age) [1]. In the US, the median age at presentation is 67 years [2]. According to Surveillance, Epidemiology, and End Results (SEER) statistics, patients older than 65 years of age encompass the majority of those diagnosed with AML [2]. Long-term survival is disproportionately worse for older patients with AML as death rates from AML are highest among adults 65 years of age and older [2]. AML is heterogeneous in terms of tumor biology, clinical presentations, and response to treatment. Compared with younger patients, older patients tend to present with lower white blood cell counts and lower

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percentage of blasts in the bone marrow, perhaps due to known or unknown pre-existing hematologic malignancies such as myelodysplastic syndrome (MDS) or myelofiborosis [3]. Outcomes are quite poor for elderly patients, largely due to host-related factors and disease-related features that confer resistance to therapies, resulting in higher rates of induction failures, relapse, and a median overall survival (OS) of less than 1 year, thus making the optimal management of elderly patients with AML unclear. Moreover, the treatment of older patients with relapsed or refractory AML is particularly poor, and effective treatment options for these patients are limited [4]. The purpose of this review was to highlight the currently available strategies, as well as future strategies under clinical development, that are available for treating older patients with relapsed or refractory AML.

2 Previously Untreated Acute Myeloid Leukemia (AML)

Standard remission induction chemotherapy for AML patients (except acute promyelocytic leukemia) younger than 60 years of age and older patients who are medically fit with low- or intermediate-risk disease consists of 3 days of an anthracycline (idarubicin or daunorubicin) combined with 7 days of cytarabine (3 + 7), followed by post-remission therapy with one to four cycles of high-dose cytarabine and/or allogeneic hematopoietic stem cell transplant (HCT) [5, 6]. With standard induction therapy, 60–80 % of young adults and 40–60 % of older adults with newly diagnosed AML will achieve a complete remission (CR) [7, 8]. Lower rates of remission in older adults are also attributed to increased frequencies of unfavorable cytogenetics (Table 1) and multidrug resistance-1 (MDR1) protein expression [9, 10]. Other factors that contribute to unfavorable clinical outcomes include older age and poor performance status (PS) [10–12]. Although chronological age alone is not necessarily a good surrogate marker for predicting tolerability to standard treatment, older patients tend to have comorbidities that contribute to higher rates of treatment-related mortality following standard induction therapy [7, 10, 13, 14]. In one study, rates of treatment-related mortality exceeded 30 % in elderly patients following standard induction therapy [15]. Furthermore, older patients with AML tend to have a higher frequency of secondary leukemias, pre-existing hematologic malignancies (i.e. MDS or myelofiborosis), multidrug-resistant gene expression (MDR1), and adverse cytogenetics, all of which contribute to drug resistance [7, 16, 17]. Although CR rates have been reported to be as high as 60 % for this population, median OS for this group ranges from 7 to 12 months, and only 10 and 2 % of patients are alive at 2 and 5 years after diagnosis, respectively [16, 18–22]. Compared with cytogenetically normal (CN) AML, or those expressing an adverse karyotype, older patients expressing core-binding factor (CBF) alterations, namely t(8:21), inversion 16 [inv(16)] and t(16:16), have CR rates of 90 % and cure rates of 50–80 % [23]. However, CBF-AML accounts for only approximately 12–15 % of all AML cases in adults, and the frequency of t(8;21) and inv(16) in older patients decreases [23]. In addition to cytogenetic abnormalities, several molecular abnormalities have been identified that impact prognosis, particularly within the context of CN AML.

3 Impact of Molecular Abnormalities

Although adult patients with no identifiable cytogenetic abnormalities are considered as having an intermediate prognosis, some somatically-acquired mutations will impact prognosis. For instance, a subgroup of CN patients who harbor somatic mutations such as nucleophosmin (*NPM1*) and CCAAT/enhancer binding protein-α (*CEBPA*) genes trend toward favorable outcomes for both younger and older patients (Table 1) [9]. However, the presence of *NPM1* mutations have been reported to occur less frequently in elderly patients and are associated with reduced CR rates and survival compared with younger patients [9]. In addition, activating mutations involving fms-like tyrosine kinase-3 (*FLT3*) are common in older patients and confer a particularly poor prognosis. Recently characterized somatic mutations in DNA methyltransferase 3A (DNMT3A), tet methylcytosine dioxygenase 2 (TET2), and isocitrate dehydrogenase (IDH) are believed to be linked to aberrant DNA methylation patterns in AML [24, 25]. The prognostic implications of TET2 and IDH are not clearly established; however, DNMT3A mutations, in particular, are associated with hyperleukocytosis at disease presentation, elderly age, and poor prognosis. Although associated with a poor prognosis, DNMT3A-mutated AML may benefit from treatment with hypomethylating agents [26]. These epigenetic-modifying mutations occur frequently in CN AML and are often retained at relapse, thus suggesting a functional role in the pathogenesis of AML. In addition, some of these molecular abnormalities may be viable therapeutic targets and/or serve as reliable indicators of residual disease.

4 Relapsed/Refractory AML

Relapsed and refractory AML is associated with an extremely poor prognosis, particularly for the elderly. Treatment of relapsed or refractory AML patients is considerably less

Table 1 ELN primary AML risk stratification and predicted outcomes by karyotype and age at 3 years [9]

ELN group	Karyotype	Incidence (%)		CR (%)		DFS (%)		OS (%)	
		<60 years	≥60 years	<60 years	≥60 years	<60 years	≥60 years	<60 years	≥60 years
Favorable	t(8;21)	41	20	96	83	55	24	66	33
	inv(16) or t(16:16); *CBFB-MYH11*								
	Diploid with *CEBPA*-mutated or *NPM1*-mutated without *FLT3*–ITD								
Intermediate I	Diploid with *NPM1*-mutated and *FLT3*–ITD	18	19	76	61	23	10	28	11
	Diploid with *NPM1*-wt and *FLT3*–ITD								
	Diploid with *NPM1*-wt without *FLT3*–ITD								
Intermediate II	t(9;11)(p22;q23); *MLLT3-MLL*, cytogenetic abnormalities not classified as favorable or adverse	19	30	79	63	34	11	45	16
Adverse	Complex karyotype,[a] −5, del(5q), −7, t(6;9)(p23;q34); *DEK-NUP214,* abn(17p), inv(3)(q21q26.2) or t(3;3)(q21;q26.2);*RPN1-EVI1,* t(v;11)(v;q23); *MLL* rearranged	22	31	50	39	10	6	12	3

AML acute myeloid leukemia, *CR* complete remission, *DFS* disease-free survival, *ELN* European LeukemiaNet, *FLT3–ITD* internal tandem duplication of the fms-like tyrosine kinase-3, *NPM1* nucleophosmin 1, *OS* overall survival, *wt* wild-type

[a] Complex karyotype containing three or more cytogenetic abnormalities in the absence of one of the WHO-designated recurring translocations or inversions: t(8;21), inv(16) or t(16;16), t(15;17), t(9;11), t(v;11)(v;q23), t(6;9), inv(3) or t(3;3)

Table 2 Strong independent clinical and biological adverse prognostic factors for AML patients in first relapse

Factor	EPI [34]	GOELAMS [35]
CR1 duration	≤6 months	<12 months
Karyotype at diagnosis	Intermediate/adverse cytogenetics	High risk
Age at relapse (years)	Older than 45	–
Prior allogeneic HCT	Yes	–
FLT-3 status	–	Positive

AML acute myeloid leukemia, *CR1* first complete remission, *EPI* European Prognostic Index, *FLT-3* fms-like tyrosine kinase-3, *GOELAMS* Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang, *HCT* hematopoietic stem cell transplant

successful, especially in the elderly [27–30]. The probability of achieving a second CR (CR2) depends heavily on the duration of the first CR [27, 31]. For example, CR rates for patients refractory to induction chemotherapy or who relapse within 12 months are discouraging (10–30 %), whereas CR rates for patients with a remission lasting greater than 12 months are approximately 40–70 %. Although attainment of CR is quite possible, the median duration of the second relapse-free interval is generally considerably shorter than that of the first interval [32]. In fact, the overall chance of long-term remission is very low (<5 % with intensive chemotherapy) [27]. Factors noted by investigators that have a significant influence on the duration of a second remission include age, initial pretreatment cytogenetics, and the length of first remission (Table 2) [27, 33–35]. With the currently available armamentarium,

the aim of salvage therapy for many older patients is durable control of their disease or end-of-life palliation with low-intensity therapies. Responses achieved with less intense strategies tend to be less robust than conventional strategies and aim more towards control of leukemia rather than cure.

5 Approach to Treatment Decision

Intensive salvage therapy for refractory/relapse AML can be offered to medically fit older patients with the aim of achieving a second CR2 either before or after allogeneic HCT [36]. Although selected older patients can benefit from intensive therapy, as a group they are more vulnerable to treatment-related toxicities and poor outcomes [3, 16, 18, 37, 38]; however, determining the optimal salvage therapeutic approach is particularly challenging. To guide treatment strategies for individuals older than 60 years of age with untreated AML, several prognostic factors have been identified and risk scores have been proposed based on chronological age, oncology PS comorbidities, and tumor biology (cytogenetics, molecular markers, and laboratory parameters) [15, 39–41]. The German AML Cooperative Group develop an algorithm that has been validated based on data from a large study involving 1406 previously untreated elderly patients [41]. Factors associated with CR rates and early treatment-related death were body temperature, age, de novo leukemia versus leukemia secondary to cytotoxic treatment or an antecedent hematological disease, hemoglobin, platelet count, fibrinogen, and serum concentration of lactate dehydrogenase.

Recently, the value of pretreatment geriatric assessments with a focus on cognitive and physical function has been shown to improve prediction of survival among older adults treated for AML [42]. Specifically, among patients in this study considered to be medically fit for intensive chemotherapy by standard oncology assessment, poor cognitive function or low physical performance at baseline were shown to correlate with significantly lower rates of survival and a 2.5-fold higher risk of deaths [42]. However, the investigators noted that the relatively small, single-institution cohort studied was as a major limitation of the study and therefore the results must be interpreted cautiously. To our knowledge, there are no validated screening tools available for elderly patients with relapsed/refractory AML that provide prognostic stratification. Although not specific for AML, National Comprehensive Cancer Network (NCCN) guidelines for 'Senior Adult Oncology' recommend a geriatric assessment that may identify cancer patients most vulnerable to the toxicities of chemotherapy [43].

6 Aim of High-Intensity Strategies

High-intensity strategies for treating relapsed or refractory AML may consist of intermediate to high doses of cytarabine (i.e. $\geq$1000 mg/m^2) in combination with a purine nucleoside analog and/or an anthracycline. The aim of these strategies was to achieve a CR in preparation for consolidation with an allogeneic HCT, since allogeneic HCT is the only modality that provides a chance for cure. Due to the potential toxicities associated with these regimens, high-intensity chemotherapy should be reserved for medically fit individuals.

6.1 Purine Nucleoside-Based Combination Regimens

Many chemotherapeutic agents, other than the standard anthracyclines and cytarabine, have been reported as having activity in relapsed AML. Purine nucleoside analogs (PNAs), namely fludarabine (FAMP), cladribine (2-Cda), and clofarabine, represent a group of cytotoxic drugs routinely used for the treatment of lymphoproliferative disorders that have activity against AML refractory to conventional treatment [44–46]. Structurally similar to natural nucleosides, PNAs compete with the role of natural nucleosides during DNA and RNA synthesis. Once incorporated in DNA and RNA, PNAs inhibit several intracellular enzymes (e.g, ribonucleotide reductase and DNA polymerases) involved with DNA synthesis and repair [47–50]. Although these PNAs have activity in the salvage setting as a single agent, they are most effective when combined with cytarabine for the treatment of myeloid malignancies [51, 52]. Both preclinical studies and clinical studies have demonstrated synergistic interactions between FAMP, 2-CdA or clofarabine and cytarabine, whereby these PNAs potentiate the intracellular accumulation of cytarabine, resulting in increased cytotoxic effect and enhanced efficacy [44–46, 53, 54]. Furthermore, the addition of granulocyte colony-stimulating factor (G-CSF) may also enhance cytarabine-mediated toxicity [55]. Examples of salvage strategies using commercially available agents with an acceptable toxicity profile that have demonstrated promising activity in patients with relapsed or refractory AML are shown in Table 3.

6.2 Role of Hematopoietic Stem Cell Transplant

Ideally, the treatment of individuals with relapsed/refractory AML with intensive chemotherapy should involve stem cell transplant, given that allogeneic HCT is only a curative option for relapsed or refractory AML. Recent

Table 3 Examples of commercially available salvage regimens for elderly patients with AML

References	Regimens	*N*	Median age,[a] years (range)	CR [*n* (%)]	Survival of relapsed/refractory patients
Intensive strategies					
Jabbour et al. [106]	FAMP + Ara-C bid (*BIDFA*)	93	62 (19–85)	21 (23)	Age >60 years; at 6 months EFS = 9 %, OS = 29 %
Montillo et al. [107]	FAMP + Ara-C + G-CSF (*FLAG*)	38	41 (11–70)	21 (55.3)	Estimated mOS = 9 months; mDFS = 12 months
De la Rubia et al. [108]	FAMP + Ara-C + G-CSF + IDA (*FLAG-IDA*)	45[b]	59 (18–79)	12 (53)[c]	At 12 months OS = 40 %
Robak et al. [109]	2-CdA + + Ara-C + G-CSF (*CLAG*)	20	44 (20–62)	10 (50)	All: mOS: 24 weeks (1.0–96.3) CR: mOS: 36.1 weeks (3.5–96.3)
Martin et al. [110]	2-CdA + + Ara-C + G-CSF (*CLAG*) or 2-CdA + Ara-C + MIT (*CLAM*)	5/4	63 (23–80)	2 (40)/2 (50)	CLAG deaths:[d] 43 % CLAM deaths:[d] 0 %
Wrzesień-Kuś et al. [111]	2-CdA + Ara-C + G-CSF (*CLAG*)	58	45 (18–67)	29 (50)	mOS for CR: 59 weeks (4–206+) mDFS: 17 weeks (1–202+)
Wierzbowska et al. [112]	2-CdA + + Ara-C + G-CSF + MIT (*CLAG-M*)	43	44 (20–66)	21 (49)	mOS: 43 weeks (3–174+) mDFS: 26.2 weeks (0.5–138+)
Becker et al. [113]	Clofarabine + Ara-C + G-CSF (*GCLAC*)	50	53 (19–69)	21 (49)[e]	mOS: 9 months; 17 patients alive after a median follow-up of 1.9 years
Faderl et al. [114]	Clofarabine + Ara-C (CA) or Ara-C alone	162/158	67 (55–86)	57 (35.2)/28 (17.8)	CA vs. Ara-C mOS: 6.6 months vs. 6.3 months ($p = 1.00$) 30-day mortality: 16 vs. 5 %
Low-intensity strategies					
Al-Ali et al. [58]	Azacitidine	20	72 (32–84)	0[f]	mOS: 2.9 months (0.7–NR)
Ivanoff et al. [59]	Azacitidine	47	63 (29–79)	10 (21)	Relapse <12 months: mOS of 7.4 months Relapse >12 months: mOS of 11 months
Ritchie et al. [60]	Decitabine	102	66 (21–88)	16 (15.6)	mOS of 177 days
Ravandi et al. [74]	Azacitidine + sorafenib	43	64 (24–87)	16 (43)	Nonresponders: mOS of 6 months Responders: mOS of 7.8 months
Jensen et al. [115]	LD Ara-C	25	47 (15–61)	11 (44)	Two patients ≥60 years: 5 months

AML acute myeloid leukemia, *Ara-C* cytarabine ≥1 g/m^2/day, *bid* twice-daily, *CR* complete remission, *EFS* event-free survival, *FAMP* fludarabine, *G-CSF* granulocyte colony-stimulating factor, *HI* hematologic improvement, *IDA* idarubicin, *LD Ara-C* low-dose cytarabine (10 mg/m^2/day subcutaneously for 21 days), *mDFS* median disease-free survival, *MDS* myelodysplastic syndrome, *MIT* mitoxantrone, *mOS* median overall survival, *N* population of relapsed/refractory patients with AML, *NR* not reached, *OS* overall survival

[a] Median age of all patients enrolled in the study

[b] Includes 13 high-risk MDS patients

[c] Authors did not observe significant differences in terms of CR between patients above or below 60 years of age, suggesting a useful alternative for medically fit elderly patients

[d] During periods of aplasia

[e] Forty-three patients were evaluable for response

[f] Although no CRs, 10 % achieved an HI and 50 % stable disease

efforts have focused on consolidating elderly patients with reduced-intensity conditioning (RIC) regimens, which are associated with a lower incidence of toxicities and are potentially curative treatment options for elderly patients with AML who would otherwise not be candidates. Early identification of donor may be necessary given that the

durability of responses gained from most salvage regimens are usually short-lived.

7 Aim of the Low-Intensity Approach

Low-intensity strategies are generally reserved for patients medically unfit for induction and consolidation with intensive chemotherapy. Low-intensity regimens aim to reduce treatment-related mortality and improve quality of life through improved control of disease. The low-intensity salvage options that do exist for elderly patients essentially consist of hypomethylating agents, and palliative strategies with low and phase I/II investigational agents. Examples of commercially available agents are provided in Table 3.

7.1 First-Generation Hypomethylating Agents

A group of agents that has received substantial attention for the treatment of older patients with AML are DNA hypomethylating agents. The hypomethylating agents azacitidine and decitabine are nucleoside analogs that restore expression of tumor suppressor genes silenced by hypermethylation of DNA by inhibiting DNA methyltransferase, an enzyme that catalyzes the addition of a methyl group to cytosine in CpG residues in DNA. Hypomethylating agents have demonstrated improved outcomes in MDS and are well-tolerated alternatives to intensive chemotherapy for older patients who are unwilling or medically unfit to receive intensive chemotherapy [56]. Compared with conventional care regimens, hypomethylating agents have been shown to improve survival in newly diagnosed elderly patients with unfavorable cytogenetics and low bone marrow blasts (<30 %) [56, 57]. Although widely studied in newly diagnosed AML patients, hypomethylating agents also have activity in the salvage setting. In 40 patients with relapsed/refractory AML ($N = 20$) or newly diagnosed AML ($N = 20$) deemed medically unfit for chemotherapy due to serious concomitant medical illnesses ($N = 20$), 5 consecutive days of subcutaneous azacitidine every 28 days yielded a CR, partial response (PR), or hematologic improvement (HI) in 12 patients (30 %) [58]. Among the 20 relapsed/refractory patients, 14 (70 %) individuals were 65 years of age and older. Two patients (10 %) in the older cohort achieved an HI, and 10 (50 %) achieved disease stability. The median duration of response of the relapsed/refractory group was 4.5 months. Among the 20 newly diagnosed patients, 10 (50 %) individuals achieved a CR, PR, or HI that lasted a median of 5.9 months (range 1 to 'not reached'). After a median follow-up of 13 months (range 9–16), newly diagnosed patients had a median survival time of 7.7 months (range 0.2 to 'not reached'), with an estimated 1-year survival of 39 %, whereas patients with relapsed or refractory AML had a median survival of 2.9 months (range 0.7 to 'not reached'). In a small, retrospective analysis of 47 patients with relapsed or refractory AML treated with 5-azacytidine (75 mg/m^2 subcutaneously for 7 days) after at least one course of intensive chemotherapy in three different French institutions, 10 (21 %) achieved a CR, 5 (11 %) achieved a PR, and 3 (6 %) achieved an HI, for an overall response rate (ORR) of 38 % [59]. Median time to relapse was 6 months (range 1–39). Median OS was 9 months (not reached by responders vs. 4.5 months for nonresponders; $p = 0.0001$). The median age of subjects was 63 years (range 29–79) and 59 % were older than 60 years. The authors noted a trend toward better survival in patients who relapsed after 12 months post-CR compared with those who were refractory or had relapsed less than 12 months post CR (11 vs. 7.4 months; $p = 0.19$) [59].

Recently reported by Ritchie et al., a 10-day cycle of decitabine 10 mg/m^2 yielded a CR rate of 16 % and median OS of 177 days among 102 relapsed/refractory patients [60]. In the newly diagnosed cohort, repeated 10-day cycles of decitabine produced a CR in 40 patients. Median OS of the newly diagnosed cohort was 318 days, but responders' survival was prolonged (481 days). In summary, hypomethylating agents have demonstrated activity in the salvage setting; however, responses to single-agent hypomethylating agents in the salvage setting tend to be of short duration.

7.2 Second-Generation Hypomethylating Agents

SGI-110 is a second-generation hypomethylating agent that is currently being tested in phase I/II clinical trials in humans with MDS, AML, and solid tumors. SGI-110 is a dinucleotide antimetabolite of decitabine linked by a phosphodiester bond to a guanosine with increased in vivo exposure of decitabine due to increased protection from deamination [61]. SGI-110 delivers decitabine with a fourfold longer half-life and overall exposure of up to 8 h (twofold longer than intravenous decitabine) [61]. Recent data from a phase I study in patients with relapsed/refractory intermediate- or high-risk MDS and AML determined the lowest effective dose for inducing maximum demethylation, as measured by long interspersed nuclear element-1, was 60 mg/m^2 daily subcutaneously for 5 days [61]. Data from a phase II study of SGI-110 in 50 heavily pretreated patients with relapsed/refractory AML using a standard 5-day regimen every 28 days showed an overall CR rate, including CR with incomplete platelet recovery (CRp) and CR with incomplete blood count recovery (CRi), of 16 % [62]. Recently, Griffith et al. also reported on a 10-day subcutaneous regimen using 60 mg/m^2/day of

SGI-110 on days 1–5 and 8–12 every 28 days for at least two to four cycles, followed by 60 mg/m^2/day on days 1–5 every 28 days for a total of at least six cycles [63]. Among 53 heavily pretreated AML patients with a median age of 57 years (range 29–82), seven (13 %) patients achieved a CR, three (6 %) achieved a CRp, and six (11 %) achieved a CRi, for an overall CR rate of 30 %. Median duration of response was 163 days (42– 274+), and median OS was 211 days (95 % CI 169–266). Mortality rates by days 30 and 60 were 1.9 % and 11.3 %, respectively. Thus far, SGI-110 seems to be a well-tolerated hypomethylating agent. The most common grade 3 or higher adverse events (AEs) have been febrile neutropenia, thrombocytopenia, anemia, leukopenia, neutropenia, and pneumonia. An ongoing phase II dose-expansion study is evaluating the efficacy of SGI-110 in four cohorts of patients: relapsed/refractory AML, relapsed/refractory MDS, frontline elderly AML not suitable for induction chemotherapy, and frontline MDS (NCT01261312).

7.3 Vosaroxin

Vosaroxin (formerly voreloxin; SNS-595) represents a novel, first-in-class naphthyridine analog that is structurally related to quinolone antibacterials with promising cytotoxic activity in AML [64]. Vosaroxin is mechanistically similar to anthracyclines, in that it induces site-specific DNA damage by intercalating DNA and inhibiting topoisomerase II, leading to G2 arrest and apoptosis [65]. Since it is not a substrate for P-glycoprotein and its cytotoxic activity is independent of p53, vosaroxin evades important mechanisms of resistance [66]. Unlike anthracyclines, vosaroxin does not appear to generate substantial reactive oxygen species (ROS), thus potentially decreasing the risk of cardiotoxicity [67]. A unique characteristic, this drug lends itself to being a particularly attractive cytotoxic agent for the treatment of AML.

In phase I and II studies, vosaroxin has shown promising activity and tolerability in elderly patients with AML, as a single agent or in combination with cytarabine or decitabine. Vosaroxin is undergoing testing in combination with decitabine in older patients with newly diagnosed AML and high-risk MDS in a phase I/II study [NCT01893320]. Recently, Daver and colleagues reported on data on 35 patients (32 with AML, 3 with high-risk MDS) with a median age of 71 years (range 41–78) treated with vosaroxin and decitabine [68]. Among the 35 patients enrolled in the study, 15 (43 %) harbored diploid cytogenetics, 12 (34 %) had complex cytogenetic abnormalities, including chromosome 5 and/or 7 abnormalities, and 8 (23 %) had other miscellaneous abnormalities. The first 24 patients were treated with vosaroxin 90 mg/m^2 daily on days 1 and 4 with decitabine 20 mg/m^2 daily for 5 days. Due to mucositis, the dose of vosaroxin was subsequently reduced from 90 to 70 mg/m^2 beginning with the 25th patient. Among 34 patients evaluable for response, 17 (50 %) achieved a CR, 6 (18 %) achieved a CRp, and 3 (9 %) achieved a CRi, for an ORR of 77 %; one patient was too early for response assessment. Noteworthy were the ORRs observed in patients aged 60–70 years (88 %), older than 70 years (71 %), and those harboring a P53 mutation (67 %). According to investigators, the regimen was well-tolerated. Grade 3 or higher mucositis occurred in only nine (26 %) patients and liver enzyme elevation in three (9 %) patients. Mortality at 4 and 8 weeks was 0 % and 14 %, respectively [68].

Data from the pivotal phase III, randomized, double-blind VALOR trial exploring vosaroxin plus cytarabine in patients with first-relapse or refractory AML were recently reported by Ravandi et al. [69]. In this trial involving 124 sites, 711 patients with relapsed or refractory AML were randomized 1:1 to receive cytarabine (1000 mg/m^2 intravenously over 2 h on days 1–5) plus either vosaroxin 90 mg/m^2 intravenously over 10 min on days 1 and 4 and 70 mg/m^2 in subsequent cycles (n = 356), or placebo (n = 355) [69]. The primary endpoint was OS and the secondary endpoints were CR rates, safety, event-free survival (EFS), leukemia-free survival (LFS), and transplantation rate. Although, in this trial, an OS advantage was not realized with vosaroxin combination compared with placebo and cytarabine (7.5 vs. 6.1 months, respectively; hazard ratio [HR] 0.865; p = 0.06), a planned predefined analysis censoring for subsequent transplant revealed an improved median OS with vosaroxin and cytarabine compared with placebo and cytarabine (6.7 vs. 5.3 months; HR 0.81; 95 % CI 0.67–0.97; p = 0.02; stratified p = 0.03) [69]. The median OS among subjects 60 years of age and older was also significantly improved with vosaroxin compared with placebo (7.1 vs. 5 months; HR 0.755; p = 0.006). However, OS was not significantly different among patients who were younger than 60 years of age (9.1 vs. 7.9 months; HR 1.08; p = 0.60), with refractory disease (6.7 vs. 5.0 months; HR 0.87; p = 0.23), and with late relapse (14.1 vs. 12.3 months; HR 0.98; p = 0.96) [69]. The CR rate (secondary endpoint) with vosaroxin combination was significantly better than placebo (30.1 vs. 16.3 %; $p < 0.0001$). Despite the advanced age of the subjects, the 30-day and 60-day all-cause mortality was similar between the two arms (30-day: 7.9 vs. 6.6 %; 60-day: 19.7 vs. 19.4 %, with vosaroxin/cytarabine vs. placebo/cytarabine) [69]. The most common serious adverse experiences were febrile neutropenia (11.3 % with vosaroxin combination vs. 7.4 % with placebo and cytarabine), sepsis (8.7 vs. 4.3 %), pneumonia (7.6 vs. 4.9 %), bacteremia (8.5 vs. 2.9 %), and stomatitis (3.4 vs. 1.4 %).

8 Receptor Kinase Inhibitors

In addition to cytotoxic therapies and hypomethylating agents, an increasing array of small molecule tyrosine kinase inhibitors are under development that target specific genetic and biochemical alterations involved in the proliferation and survival of leukemia cells. Among these are a group of inhibitors that target *FLT3*, a receptor tyrosine kinase (RTK) expressed on the surface of hematopoietic stem and progenitor cells that plays an important role in the normal development of stem cells and the immune system. Mutations involving *FLT3* are a growing concern for clinicians. The most common activating mutations of *FLT3* are internal tandem duplications (ITD) that occur within the juxtamembrane domain of the receptor. *FLT3*–ITD mutations occur in roughly 25 to 30 % of de novo adult AML, resulting in shorter durations of remission and higher rates of relapse [70, 71]. In patients older than 65, the reported incidence of *FLT3*–ITD is approximately 27 % [72]. These mutations are often associated with normal karyotypes, leukocytosis, elevated bone marrow and peripheral blasts, and early relapse [70, 73, 74]. Because of its prevalence in AML and negative impact on survival, *FLT3*–ITD has emerged as one of the most attractive therapeutic targets in AML. Indeed, several small molecule inhibitors targeting *FLT3* mutations are currently being explored, and include sorafenib, quizartinib (formerly known as AC220), crenolanib, and gilteritinib (formerly known as ASP2215). In addition to targeting *FLT3*–ITD, crenolanib also has activity against point mutations that occur at residue D835 within the activation loop of the receptor. Albeit, this mutation occurs in approximately 7 % of de novo adult AML, and its prognostic significance is unclear [72]. Similarly, gilteritinib uniquely targets the AXL kinase, an RTK that is overexpressed in many solid tumors and hematologic malignancies, and contributes to the pathogenesis of *FLT3*–ITD-positive AML [75]. Unique in its molecular target is volesertib, a selective inhibitor of human polo-like kinase-1 (PLK1), a key regulator of mitosis that is also overexpressed in solid tumors and hematologic malignancies.

8.1 Sorafenib

Sorafenib is a multikinase inhibitor with activity against *FLT3* and several RTKs, including RAF kinase, vascular endothelial growth factor receptor-2 (VEGFR2), platelet-derived growth factor receptor (PDGFR), Ret, and c-Kit. Its use as an *FLT3* inhibitor for AML has been studied off-label since the FDA indication for sorafenib is limited to the treatment of unresectable hepatocellular cancer, advanced renal cell carcinoma, and locally recurrent or metastatic, progressive, differentiated thyroid cancer (refractory to radioactive iodine treatment). In the salvage setting, sorafenib monotherapy has been shown to provide meaningful clinical responses in *FLT3*–ITD-positive patients. In a phase I clinical trial involving 16 previously treated patients with AML, a clinical response was observed in nine (56 %) patients, eight of whom were older than 60 years of age (range 61–81 years) [76]. Among seven patients in the same study with *FLT3*–ITD, sorafenib was found to be markedly active in six patients [76]. Metzelder et al. described achievement of a clinically meaningful response with compassionate use of sorafenib monotherapy in four of six patients following allogeneic HCT relapse, two of whom achieved a complete molecular response [77]. Results from several case reports have also described rapid clearance, or near clearance, of blasts in relapsed or chemorefractory *FLT3*–ITD-positive patients [77, 78]. In combination with hypomethylating agents, sorafenib has also demonstrated promising efficacy. In a phase II study with azacitidine and sorafenib in patients with AML (median age 64 years) and *FLT3*–ITD, 6 of 37 evaluable patients (16 %) achieved a CR, 10 (27 %) achieved a CRi, and 1 (3 %) achieved a PR, for an ORR of 46 % [74]. The median OS for responders and nonresponders was 7.8 and 6 months ($p = 0.01$), respectively. Despite the remarkable responses achieved in this difficult-to-treat population, the median duration of response in this trial was only 2.3 months (range 1–14.3 months). In the salvage setting, sorafenib is generally well-tolerated, sparing patients of toxicities associated with intensive chemotherapy. As monotherapy or in combination with hypomethylating agents, sorafenib may be useful for gaining temporary control of *FLT3*-ITD positive leukemia. In some case, sorafenib may also serve as bridge therapy to allogeneic HCT for eligible patients.

8.2 Quizartinib

Quizartinib is a second-generation *FLT3* inhibitor with high potency and selectivity for *FLT3* kinase in AML [79]. Quizartinib monotherapy first demonstrated remarkable clinical activity in heavily pretreated (a median of three prior treatments) relapsed/refractory elderly patients with AML irrespective of *FLT3* status in a phase I study conducted by Cortes et al. [80]. In this study, the ORR response rate in the *FLT3*–ITD-positive patients was higher than *FLT3*–ITD-negative patients—53 % (one CR, one CRp, two CRis, five PRs) versus 14 % (two CRps, three PRs). However, the median duration of response was shorter in the *FLT3*–ITD-positive patients compared with the *FLT3*–ITD-negative group (10 vs. 24 weeks). In a phase II study, 54 % of elderly patients (median age

70 years; range 54–85 years) with relapsed/refractory *FLT3*–ITD AML achieved a composite CR, and the median duration of response and OS was 12.7 and 25.3 weeks, respectively [81, 82]. Quizartinib can also be safely combined with chemotherapy agents. Borthakur and colleagues recently reported on a phase I/II study investigating the combination of quizartinib (60 mg/day [dose level 1] or 90 mg/day [dose level 2]) with cytarabine (20 mg subcutaneously twice daily for 10 days of every cycle) or azacitidine (75 mg/m^2 subcutaneously or intravenously for 7 days of every cycle) in patients with relapsed/refractory and previously untreated high-risk MDS, chronic myelomonocytic leukemia (CMML), and AML [83]. Among 26 patients enrolled in the study, 5 in cytarabine arm (63 %) and 13 (72 %) in the azacitidine arm responded to therapy [83]. The median time to response was 57 days (range 25–102 days). Overall, the combination strategies were well tolerated.

8.3 Crenolanib

With the development of *FLT3* inhibitors, reports of resistance-conferring tyrosine kinase domain mutations are a growing concern for clinicians, and were recently reported to occur in up to 22 % of patients during *FLT3*–TKI therapy, and were associated with disease progression [84]. Indeed, evolution of *FLT3*/D835 mutations are presenting new clinical challenges and driving the development of RTK inhibitors that target FLT–ITD and *FLT3*/D835 mutations. Crenolanib represents a next-generation RTK that has activity against both *FLT3*–ITD and *FLT3*/D835 point mutants, including *FLT3*–TKI failures [85]. Several trials exploring crenolanib in relapsed/refractory *FLT3*-positive AML (*FLT3*–ITD, *FLT3*–D835, *FLT3*–ITD/D835) are ongoing (NCT01522469, NCT01657682). Data from a phase II trial in heavily pretreated relapsed/refractory AML patients (median of 3.5 prior therapies [range 1–8]) with activating *FLT3* mutations were recently reported [86]. Among 38 patients enrolled in two parallel cohorts in the study, 13 were *FLT3* inhibitor-naïve and 21 did not respond to at least one *FLT3* inhibitor. Among 34 evaluable patients, 47 % responded to therapy (12 % achieved a CRi, 32 % achieved HI, and 3 % achieved a morphologic leukemia-free state [MLFS]). Rates of CRi were more robust in the *FLT3*–TKI-naïve group (23 %) than those who were previously treated with an *FLT3* inhibitor (5 %). For the *FLT3*–TKI-naïve group, median EFS (55 vs. 13 weeks; $p = 0.027$) and OS (13 vs. 7 weeks; $p < 0.001$) were significantly better than those previously exposed to an *FLT3* inhibitor [86]. Grade 3 toxicities were limited to gastrointestinal side effects, such as nausea and abdominal pain.

8.4 Gilteritinib

Gilteritinib (formerly known as ASP2215) is another orally bioavailable RTK that has demonstrated promising antileukemia activity against nonclinical AML models harboring *FLT3*–ITD, *FLT3*–D835 mutations or both [87]. Gilteritinib potently inhibits multiple tyrosine kinases, primarily *FLT3*, AXL, and anaplastic lymphoma kinase (ALK or CD246). Overexpression of these receptor kinases or mutations contributes to tumor cell growth and survival, thus serving as attractive targets. Multiple phase I/II studies exploring the effectiveness of gilteritinib in patients with relapsed or refractory AML with or without the *FLT3* mutation are ongoing (NCT02014558, NCT02181660). Other studies are combining gilteritinib with traditional chemotherapy in newly diagnosed AML (NCT02236013, NCT02310321).

8.5 Volasertib

Volasertib is another small molecule inhibitor that selectively binds to the ATP binding pocket of the human PLK1, a key regulator of mitosis. PLK1 is overexpressed in many solid tumors and hematologic malignancies, including AML. Inhibition of PLK1 preferentially blocks proliferation of leukemic rather than normal cells [88]. Volasertib is the most advanced PLK1 inhibitor in clinical development for AML. It recently received FDA breakthrough therapy designation for the treatment of AML, based on a phase II randomized study comparing volasertib and low-dose cytarabine versus low-dose cytarabine in previously untreated AML patients ineligible for intensive chemotherapy [89]. The combination of volasertib and low-dose cytarabine yielded superior objective response rates of 31 % (13 of 42 patients) versus 13.3 % (6 of 45 patients) [$p = 0.0523$] and EFS (5.6 vs. 2.3 months; HR 0.56; 95 % CI 0.34–0.93; $p = 0.0237$) compared with low-dose cytarabine [89]. Although not statistically significant, a trend towards an OS benefit (8.0 months compared with 5.2 months; $p = 0.996$) was observed. These results led to the initiation of the phase III, POLO-AML-2 trial (NCT01721876), testing the combination of volasertib plus subcutaneous low-dose cytarabine against low-dose cytarabine in older patients (≥65 years) with previously untreated AML who were ineligible for intensive remission induction therapy. This trial has closed and we are waiting for the results. In the salvage setting, volasertib is being investigated in phase I/II clinical trials as monotherapy (NCT00804856) and in combination with hypomethylating agents (NCT02003573, NCT01662505) and cytarabine-based regimens (NCT00804856).

9 Inhibitors of Isocitrate Dehydrogenase

Identification of mutations in genes encoding two isoforms of IDH (IDH1 and 2) in gliomas and AML were recently identified and because of their tendency for promoting tumorigenesis, mutated IDH1 and IDH2 enzymes are new therapeutic targets of interest [90, 91]. These gain-in-function mutations commonly affect one of three highly conserved arginine residues of the enzyme's active sites at position 132 of IDH1, and positions 172 and 145 of IDH2, disrupting the enzyme's ability to catalyze the conversion of isocitrate to α-ketoglutarate in the cytosol and mitochondria, respectively [92]. Instead, mutant IDH enzyme activity results in accumulation of a 2-hydroxyglutarate (2-HG), which may alter the epigenetic control of stem and progenitor cell differentiation [92, 93].

9.1 AG-221 and AG-120

The prevalence of IDH1 and IDH2 missense mutations among adults with primary AML is between 5 and 20 %. Interestingly, these genetic aberrances occur infrequently in pediatric AML (3.5 %) [94]. In AML, IDH2 mutations occur more frequently than IDH1 mutations. The frequency of IDH mutations strongly associates with intermediate-risk cytogenetics, *NPM1* genotypes, and myeloproliferative neoplasm-derived AML [95]. These mutations are heterozygous and virtually mutually exclusive [96]. Although the prognostic significance of IDH mutations is unclear, and how they contribute to tumorigenesis has not been fully elucidated, new agents, such as AG-221 and AG-120, that target these enzymes are under preclinical and clinical development. AG-221 is a first-in-class potent, selective, oral inhibitor of mutated IDH2. Data from the ongoing, first-in-human, phase I, open-label, dose-escalation study of AG-221 were recently reported [97]. In patients with advanced hematologic malignancies, AG-221 demonstrated sustained reductions in plasma 2-HG levels and triggered the differentiation of leukemic blast cells that ultimately led to durable responses, including CRs [97]. Approximately 90 % of patients achieved a response that lasted more than 3 months. Similar to AG-221, AG-120 is a first-in-class, oral, potent, reversible, and selective inhibitor of the mutated IDH1 protein. In a recent phase I study reported at the 26th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, held in Barcelona, Spain, AG-120 demonstrated encouraging clinical activity in AML patients harboring IDH1 mutations. In this study, 17 patients with relapsed and/or refractory AML were enrolled into one of four AG-120 dose groups: 100 mg twice daily, 300 mg once daily, 500 mg once daily, and 800 mg once daily over continuous 28-day cycles. Among 14 evaluable patients, 7 (50 %) responded to AG-120, 4 of whom achieved a CR [98]. These two agents are among several targeted therapies that are showing promise in AML and have been awarded FDA fast-track designations.

10 Anti-CD33 Monoclonal Antibodies

10.1 Gemtuzumab Ozogamicin

Monoclonal antibodies have been explored clinically for the treatment of AML for several years. The majority of monoclonal antibodies under development for AML target the CD33 antigen, which is expressed on the surface of myeloblasts in approximately 90 % of patients with AML [99]. In fact, the only monoclonal antibody approved for AML was gemtuzumab ozogamicin. Approved in 2000 for CD33-positive AML in first-relapse patients 60 years of age or older and not considered candidates for intensive chemotherapy, gemtuzumab ozogamicin contains a derivative of the antitumor antibody calicheamicin linked to a humanized monoclonal antibody directed against the CD33 antigen [100]. The approval of gemtuzumab ozogamicin was based on pooled data from three open-label, single-arm, phase II trials in patients with relapsed AML in which 57 % (n = 157) of patients were aged 60 years or older [101]. Gemtuzumab ozogamicin therapy in patients aged younger than 60 and 60 years or older resulted in an overall remission rate of 28 % (n = 33) and 24 % (n = 38), respectively. The median OS was 5.3 and 4.5 months for patients aged younger than 60 and 60 years or older, respectively. For patients aged 60 years or older in CR or CRp, the median OS was 11.7 and 11.4 months, respectively.

In June 2010, gemtuzumab ozogamicin was removed from the market due to safety concerns and failure to demonstrate clinical benefit in patients enrolled in the Southwest Oncology Group (SWOG) S0106 clinical trial. However, interest in gemtuzumab ozogamicin is making a resurgence in AML on the strength of new data. Starting with the AML-19 trial, gemtuzumab ozogamicin significantly improved OS compared with best supportive care in newly diagnosed elderly patients with AML who were not considered fit for intensive chemotherapy [102]. In the ALFA-0701 study, fractionated doses of gemtuzumab ozogamicin in combination with daunorubicin and cytarabine significantly improved EFS and relapse-free survival in adult AML patients at 3 years compared with chemotherapy alone [103]; however, a significant improvement in OS was not observed in the trial.

10.2 SGN-CD33A

SGN-CD33A is another humanized monoclonal antibody directed against CD33 that is currently in phase I clinical trials for AML. SGN-CD33A uses a potent cytotoxic DNA crosslinking pyrrolobenzodiazepine dimer conjugated to the antibody through engineered cysteine to deliver its antileukemia activity [104]. In preclinical studies, SGN-CD33A antileukemia activity is more potent than gemtuzumab ozogamicin, and antileukemic activity is observed with SGN-CD33A in AML cell samples and mouse models despite multidrug resistant (MDR) phenotype or unfavorable karyotypes [104]. In a recent open-label, phase I, dose-escalation study, 40 patients (median age 75 years [range 27–86]) with first-relapse AML ($N = 20$) or newly diagnosed AML ($n = 20$) were treated with SGN-CD33A at 5 μg/kg ($n = 3$), 10 μg/kg ($n = 3$), 20 μg/kg ($n = 13$), 40 μg/kg ($n = 18$), and 60 μg/kg ($n = 3$) [105]. Among 38 evaluable patients, 16 (42 %) experienced clearance of marrow blasts across all dose levels. At 40 μg/kg, 8 of 17 patients experienced clearance of marrow blasts, 2 of whom achieved a CR, 3 a CRi, and 3 of whom achieved a morphologic leukemia-free state [105]. SGN-CD33A was reported to be well tolerated. Neutropenia (55 %) was the only grade 3 or higher adverse event reported in >10 % of patients, and the 30-day mortality was only 2.5 %, with no treatment-related deaths.

11 Conclusions

A high proportion of patients with AML relapse after frontline therapy, and the majority of these patients are older. At the present time, allogeneic HCT is the best option for consolidating relapsed/refractory AML patients; however, allogeneic HCT is unsuitable for the majority of elderly patients due to comorbidities. Although current therapeutic strategies for relapsed/refractory patients remain unsatisfactory for most patients, particularly those with more advanced age, strategies that aim for durable responses or control of their disease essentially consist of intensive strategies, such as the combination of a PNA and cytarabine for medically fit individuals, and lower intensity approaches such as demethylating agents, small molecule inhibitors, and therapeutic monoclonal antibodies that are in the early stages of clinical development. Although, these strategies may prepare a select few for stem cell transplantation, all patients with recurrent AML should be considered for clinical trials.

Compliance with Ethical Standards

Conflict of interest Jeffrey C. Bryan and Elias J. Jabbour have no conflicts of interest to declare.

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