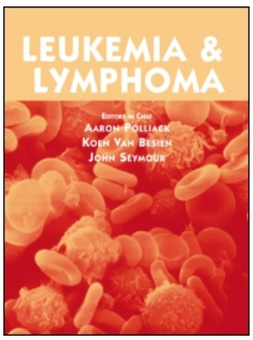

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: https://www.tandfonline.com/loi/ilal20

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To cite this article: Matteo Molica, Massimo Breccia, Saveria Capria, Silvia Trisolini, Roberto Foa, Elias Jabbour & Tapan Mahendra Kadia (2019): The role of cladribine in acute myeloid leukemia: an old drug up to new tricks, Leukemia & Lymphoma, DOI: 10.1080/10428194.2019.1672060

To link to this article: https://doi.org/10.1080/10428194.2019.1672060

Published online: 22 Nov 2019.

LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2019.1672060

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REVIEW

The role of cladribine in acute myeloid leukemia: an old drug up to new tricks

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ABSTRACT

Despite advances in understanding the pathogenesis of acute myeloid leukemia (AML), the standard therapy remained nearly unchanged for several decades. There have been many efforts to improve the response and survival by either increasing the cytarabine (ARA-C) dose or adding a third agent to the standard chemotherapy regimen. Several studies have evaluated the addition of cladribine (CdA) to standard induction, exploiting its property to potentiate ARA-C uptake. Response rates for combination regimens including CdA in relapsed/refractory (R/R) adults are approximately 50% and approximately 70% in de novo AML. Recently, a low intensity combination of CdA and ARA-C alternating with decitabine has shown promising results in older patients with AML. In this review, we will discuss the role of CdA in the treatment of AML, summarizing the recent clinical data regarding its incorporation into the induction therapy for adult AML.

ARTICLE HISTORY
Received 25 August 2019
Accepted 19 September 2019

KEYWORDS
Acute myeloid leukemia; cladribine; combination regimens

Introduction

The combination of cytarabine (ARA-C) and an anthracycline has been the standard induction regimen for patients with AML for more than 40 years. Unfortunately, in higher risk AML (patients with secondary AML, therapy-related AML, and adverse cytogenetics or mutations) the relapse rate is still over 60%, leading to an overall median disease-free survival (DFS) of <1 year (range: 4–11 months) [1,2].

Over the last several years, several studies have evaluated the addition of a third agent to standard induction chemotherapy in an effort to improve efficacy. Earlier studies adding thioguanine and etoposide were negative [3–6]. More recently, the addition of gemtuzumab ozogamicin, an antibody-drug conjugate, has been studied with promising results, mostly limited to patients with favorable-risk and intermediate-risk disease [7].

The addition of nucleoside analogs to the cytarabine-anthracycline backbone, such as cladribine (CdA), clofarabine, and fludarabine have been extensively studied and demonstrated encouraging results in this setting. Cladribine has demonstrated single-agent activity in myeloid cell lines, but is most effective in combination with ARA-C by modulating deoxycytidine kinase. This results in increasing intracellular levels of cytarabine triphosphate (Ara-CTP), which is the active antileukemic metabolite of ARA-C [8–10]. These mechanisms provide the basis for the combination of CdA with standard AML chemotherapy. Multiple studies have demonstrated that CdA combination regimens are effective both in the relapsed/refractory (R/R) setting [11–14], and more recently, for de novo AML patients [15–18]. Therefore, the National Comprehensive Cancer Network (NCCN) guidelines for AML now include CdA combination regimens as recommendation for both de novo and R/R patients with AML [19]. Furthermore, new trials including CdA combination with target therapies are ongoing, valuing the role of CdA in AML treatment.

This review discusses the mechanism of action, efficacy, and safety of CdA in managing AML.

Mechanism of action and interaction with other agents

Cladribine (2-chloro-2-deoxy-β-D-adenosine), also known as 2-CdA, is a deoxyadenosine analog

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characterized by a substitution of a hydrogen atom with chlorine at the 2-position of the purine ring with selective toxicity towards lymphocytes and monocytes. Cladribine has both single-agent and combination activity in AML; it crosses the cell membrane via equilibrative nucleoside transporter 1 and 2 as well as concentrative nucleoside transporter 3 [20], and once intracellular gets phosphorylated by dCK to 2-chloro-2′deoxy-β-D adenosine monophosphate. Subsequently, 2-chloro-2′deoxy-β-D adenosine monophosphate is converted to active triphosphate deoxynucleotides through dCK, the accumulation of which leads to cell death by interfering with DNA repair [21,22]. Cladribine may also induce cell apoptosis by both caspase-dependent [23] and caspase-independent [24] mechanisms as well as through direct mitochondrial toxicity [24,25]. The most interesting attribute of CdA is the ability to modulate the bioactivation of ARA-C by increasing intracellular levels of cytarabine triphosphate (Ara-CTP), which is the active antileukemic metabolite of ARA-C [8–10]. Gandhi et al first documented the pharmacokinetic and pharmacodynamic interactions between CdA and ARA-C, treating nine patients with AML with single dose of ARA-C 1 g/m^2 on day 1 followed by CdA 12 mg/m^2/day on days 2–6. Between day 1 (pre-CdA) and day 3 (post-CdA), a median 1.4-fold increase in both the rate of ara-CTP accumulation and the peak ara-CTP concentration was observed; the authors concluded that the metabolic potentiation of ara-CTP by CdA infusion might be responsible for sustained inhibition of DNA synthesis in the circulating leukemia blasts during therapy with this combination regimen [8]. Chow et al. assessed the interaction between ARA-C and either CdA or fludarabine in AML cells. Cytarabine and CdA were synergistic with respect to inhibition of cell proliferation, induction of apoptosis, and disruption of mitochondrial membrane potential. In contrast, the interaction between ARA-C and fludarabine was additive or antagonistic for inhibiting cell proliferation and antagonistic for induction of apoptosis [26].

Cladribine may be also acting as a hypomethylating agent through its inhibition of S-adenylhomocysteine (SAH) hydrolase; it indirectly inhibits DNA methylation by decreasing the S-adenosylmethionine (SAM) to SAH ratio through its inhibition of SAM formation. S-adenylhomocysteine excess, coupled with a deficiency of SAM, then inhibits DNA methyltransferase (DNMT), which prevents further DNA methylation [27]. Based on these findings, CdA has been also included in a protocol that alternated its combination with ARA-C and the hypomethylating agent decitabine to try to overcome potential resistance mechanisms and optimize hypomethylation in older AML patients [18].

Favorable interactions (additive or synergistic) between CdA and other chemotherapeutic agents have also been described, such as daunorubicin [28], idarubicin [29], doxorubicin [29], mitoxantrone [29], interferon-α [30,31] and interferon-γ [30].

Cladribine in relapsed/refractory AML

Several studies [32–36] studied the use of CdA, either as a single agent or in combination with idarubicin, for pediatric R/R AML (Table 1). In this setting, CdA seemed to be effective at doses ranging from 3 to 10.7 mg/m^2/day for 5 days even for the heavily pretreated pediatric patients without significant myelosuppression and neurologic toxicity. In adults, despite the maximum tolerated dose being approximately two times higher than that for children (17 mg/m^2/day), single agent CdA appeared not to be effective [40–42] with shorter remission duration than children (for example, about 23 months in the trial by Santana et al. [33] vs about 4.5 months in the trial by Kornblau et al. [40]). Based on these unsatisfactory results, subsequent studies [11–14,43–45] examined CdA combination regimens with the hope of improving outcomes in this challenging population. However, both regimens including the combination of CdA with daunorubicin [43] and with high dose ARA-C (HiDAC) [9,11] consisted in modest response rates and poor outcomes in this setting.

Table 1. Clinical studies including cladribine in pediatric patients with de novo and relapsed/refractory AML.

Study	Number of pts	De novo/R/R AML	Therapy	OS (months)	EFS (months)	CR (%)	% of pts proceeding to HSCT
Santana et al. [32]	18	R/R	CdA	NR	NR	11	NR
Santana et al. [33]	17	R/R	CdA	NR	NR	47	41
Santana et al. [37]	22	De novo	CdA	NR	NR	27	NR
Krance et al. [38]	72	De novo	CdA	NR	5 year 40%	40	71
Rubnitz et al. [34]	8	R/R	CdA + Ara-C	0	NR	NR	0
Rubnitz et al. [39]	96	De novo	CdA + Ara-C	5 year 50%	5 year 44%	53	43
Chalef et al. [36]	104	R/R	CdA + IDA	2 year 26%	2 year 20%	46	NR

pts: patients; R/R: relapsed/refractory; AML:acute myeloid leukemia; OS: overall survival; EFS: event free survival; CR: complete remission; CdA: cladribine; Ara-C: aracytin; IDA: idarubicin; NR:not reported.

To date, CLAG (CdA, ARA-C, and filgrastim) is the most promising CdA combination regimen studied in adult R/R AML. This regimen was first reported by the Polish Adult Leukemia Group (PALG) and took advantage of synergistic interactions between CdA and ARA-C and a fixed-dose of filgrastim administered 24 h before cytotoxic chemotherapy to mobilize malignant cells in the hope of increasing chemo-sensitivity. The PALG assessed CLAG regimen in 58 adults with R/R AML reporting impressive results, characterized by a complete remission (CR) rate of 50% after one or two cycles with median 1 year OS of 42% [44]. Also Price et al. later compared their single center experience with CLAG vs MEC (mitoxantrone, etoposide, and ARA-C) salvage therapy in 162 adults with R/R AML. CLAG was determined to be superior to MEC, with CR rate of 38% for CLAG vs 24% for MEC ($p = 0.048$). CLAG also showed better disease free survival (DFS) compared to MEC (6.1 months vs. 3.5 months; $p = 0.03$) and OS was favored with CLAG but did not reach statistical significance (7.3 months vs 4.5 months; $p = 0.05$) [12].

Given the success of CLAG, the PALG attempted to improve on such results by adding an additional agent, mitoxantrone, to CLAG (CLAG-M). The CLAG-M regimen was assessed in 114 patients with high risk R/R AML, including patients with primary refractory disease, relapse after an initial remission lasting <6 months, or relapse following allogeneic stem cell transplant (HSCT). Despite these poor risk features, a 58% CR rate was reported following CLAG-M induction with 39% of patients proceeding to HSCT [13].

In a recent systematic review, a total of 10 clinical trials, including 422 R/R AML patients were analyzed. The overall CR rate was 42.2%, while the ORR of seven trials including 235 patients was 49.7%. The overall early death rate of 260 patients enrolled in five trials was 6.8% [45]. A phase 2 study is ongoing at MDACC (NCT02115295) studying the efficacy of CdA 5 mg/m^2 IV given for 5 days followed by ARA-C 1000 mg/m^2 IV on days 1–5, and IDA 10 mg/m^2 IV days 1–3 in R/R AML patients. A summary of published data for CdA in RR adult AML is presented in Table 2.

Cladribine in de novo AML

The most promising combination regimen data for de novo adult AML including CdA also comes from the PALG's experience with DAC (daunorubicin: 60 mg/m^2 days 1–3, continuous infusion of ARA-C 200 mg/m^2 days 1–7 and CdA 5 mg/m^2 days 1–5). In a phase 2 trial published in 2002, the PALG reported a CR rate of 72% after DAC induction in 50 de novo adults [47]. A randomized phase 3 trial also conducted by the PALG, assessed OS differences between DA (daunorubicin and ARA-C) and DA with the addition of a purine antagonist [either CdA (DAC) or fludarabine (DAF)] in patients 60 years or younger with de novo AML. DAC regimen showed higher CR rates compared to DA (68% for DAC vs 56% for DA; $p = 0.01$), while CR rates were similar between DAF and DA (59% for DAF vs 56% for DA; $p = 0.47$). Furthermore, 3-year OS was superior with DAC compared with DA (45% for DAC vs 33% for DA; $p = 0.02$), but not DAF compared with DA (35% for DAF vs 33% for DA; $p = 0.98$). Subgroup analyses showed an advantage on OS with DAC compared with DA in patients >50 years old, with unfavorable karyotype, and with initial white blood cell count >50,000/mL [15]. Therefore, the phase III randomized PALG trial demonstrated that CdA may be more active than its purine analog counterpart fludarabine, but the study had some limitations. The DA control arm yielded a lower CR rate than would be expected. Among several published trials of induction therapy in AML, the low a CR rate seen in the PALG trial control arm was only otherwise observed in the control arm

Table 2. Clinical studies including cladribine in patients with relapsed/refractory AML.

Study	Number of pts	Therapy	OS (months)	DFS (months)	PFS (months)	CR (%)	% of pts proceeding to HSCT
Kornblau et al. [40]	27	CdA	2.6	0	0	0	NR
Vahdat et al. [41]	36	CdA	NR	NR	2.7	8	0
Gordon et al. [42]	15	CdA	1.9	0	0	0	NR
Gandhi et al. [8]	15	CdA + Ara-C	NR	NR	NR	13	NR
Kornblau et al. [40]	15	CdA + Ara-C	2.7	NR	3.4	13	
Nodehi et al. [11]	11	CdA + Ara-C	NR	NR	NR	36	NR
Van Den Neste et al. [43]	19	CdA ± DNR	1.6	0	0	0	NR
Wrzesien-Kus et al. [44]	58	CLAG	8.5	4.2	NR	50	12
Price et al. [12]	97	CLAG	7.3	6.1	NR	38	36
Wierzbowska et al. [13]	114	CLAG-M	9	17	NR	58	39
Ramsingh et al. [14]	10	CLAG + ATRA + Midostaurin	3.5	NR	NR	20	NR
Walker et al. [46]	15	CLAG + Imatinib	5.8	2.5	NR	40	7

pts: patients; OS: overall survival; DFS: disease free survival; PFS: progression free survival; CR: complete remission; CdA: cladribine; Ara-C: aracytin; DNR: daunorubicin; CLAG: CdA, Ara-C, filgrastim; CLAG-M: CdA, Ara-C, filgrastim, mitoxantrone; NR: not reported.

of an ECOG trial, in which the dose of daunorubicin was only 45 mg/m^2 per day for 3 days [48]. Other trials have used higher doses of daunorubicin in the control arm (60 mg/m^2 per day for 3 days in the SWOG study [49], 50 mg/m^2 per day for 5 days in the JALSG trial [50], and 50 mg/m^2 per day for 3 days in the MRC study [51]). In all of these studies, the results in the DA control arm demonstrated higher response rates than those observed in the DA control arm in the PALG trial, and were, in fact, at least equivalent to the outcome in the DAC arm of the PALG trial (when comparing across trials). Such differences could also be related to the bone marrow biopsy schedule included in the PALG. Common practice is to assess the bone marrow 10–14 days after induction therapy, however, the PALG did not perform a biopsy until the patient had blood count recovery that met criteria for CR, or by day 50 at the latest. Patients with peripheral blood blasts or no evidence of blood count recovery had a bone marrow evaluation at latest by day 40. This delayed assessment delayed initiation of a second induction cycle, resulting in patients who in other studies may have been considered as partial responder being considered as treatment failure patients by the PALG and therefore not candidate for a second induction cycle. Only 5% of patients achieved partial remissions from the initial induction cycle (and thus qualified for a second cycle of induction) in this study.

The PALG experience also showed as DAC regimen was effective in *FLT3-ITD+* normal karyotype AML patients compared with DA [52]. Among the *FLT3-ITD+* patients, the CR rate after DAC was 86%, whereas it was 61% after the DA regimen, with a statistically significant difference between both induction groups ($p = 0.004$). A 4-year OS advantage was also demonstrated for *FLT3-ITD+* patients treated with DAC (37%) when compared with the DA arm (14%; $p = 0.05$), with the most prominent OS improvement after censoring the observation at the time of allogeneic HSCT ($p = 0.007$).

Cladribine was also included in a triple agents combination regimen using idarubicin as the anthracycline. Fesler et al. assessed the combination of CdA with ARA-C and idarubicin (IAC) as induction regimen in 34 patients with de novo AML showing a CR rate of 62% with a median OS of 16.7 months [53]. Preliminary results of a MDACC study including data of 143 patients (among whom 51% was de novo AML) treated with CLIA regimen (CdA + ARA-C + idarubicin) have been reported [54]. In the frontline setting, overall response rate was 76% and at the time of CR, 41 (58%) patients had achieved MRD negativity by multiparameter flow cytometry. The median OS and DFS was 21.9 months and not reached, respectively. A randomized study conducted in China analyzed 27 de novo AML patients who received CdA 5 mg/m^2/day for 5 days, ARA-C 100 mg/m^2/day for 7 days, and idarubicin 8 mg/m^2/day for 3 days as induction therapy. Patients were matched by age, sex, FAB subtype, and karyotype with a control group that received ARA-C and idarubicin dosed at either 10 mg/m^2 or 12 mg/m^2. Complete remission rates were significantly improved in the CdA arm compared with the control arm given 10 mg/m^2 of idarubicin (77.8% vs 37%; $p = 0.002$) but not when compared with the control arm given 12 mg/m^2 of idarubicin (77.8% vs 63%; $p = 0.23$) [55]. In a recent publication, investigators retrospectively compared the addition of CdA to 7 + 3 (with idarubicin $n = 25$) versus standard 7 + 3 (with idarubicin, $n = 12$) [17]. After propensity score matching, odds of reaching the primary end point of CR were increased by 33% in patients who received the 7 + 3 + CdA regimen ($p < 0.01$).

The addition of another antracycline such as mitoxantrone to CdA regimens was also explored in de novo AML scenario. Standard 7 + 3 (with either daunorubicin or idarubicin ($n = 24$) was retrospectively compared with CLAG-M regimen ($n = 28$) in patients with secondary AML who received at least one cycle of azanucleoside therapy [56]. The reported CR/CRi rate (64% vs 29%; $p = 0.014$) and median OS (202 vs 62 days; $p = 0.031$) were significantly better with CLAG-M compared with 7 + 3. In addition, 21% of patients in the CLAG-M arm versus 4% of patients in the 7 + 3 arm proceeded to HSCT. Results from a recent phase II trial at the University of Washington utilizing G-CSF, HiDAC, CdA and high-dose mitoxantrone (G-CLAM) showed a high MRD-negative CR rate [57]. When the authors compared their results to historical date for patients who were treated at the same institution with 7 + 3, G-CALM resulted in better MRD-negative CR rates, but they did not find an OS advantage comparing the two arms.

In elderly setting promising results was reported by the MD Anderson group that designed a phase 2 trial based on low intensity combination of CdA and LDAC followed by consolidation with 3 days of CdA plus 10 days of LDAC alternating with decitabine [18]. One hundred and eighteen patients were enrolled, among whom 48 (41%) had an adverse karyotype, 20 (17%) had therapy-related AML, 18 (15%) had treated secondary AML, and 20 (17%) had *TP53* mutations. Eighty (68%) patients achieved objective response with a CR

Table 3. Clinical studies including cladribine in patients with de novo AML.

Study	Number of pts	Therapy	OS (months)	DFS (months)	EFS (months)	CR (%)	% of pts proceeding to HSCT
Holowiecki et al. [47]	50	DAC	NR	NR	NR	72	NR
Holowiecki et al. [15]	222	DAC	24	3-year: 45%	NR	68	NR
Fesler et al. [53]	34	IAC	16.7	NR	9.5	62	NR
Grosicki et al. [75]	DAC (30); IAC (22)	DAC; IAC	3-year: 26%; 3-year: 23%	2-year 28%; 2-year 36%	NR	70; 59	29; 20
Pluta et al. [58]	90	Low dose DAC	9.5	NR	NR	43	NR
Jaglal et al. [56]	28	CLAG-M	6.7	6.7	NR	50	21
Kadia et al. [53]	73	CLIA	21.9	Not reached	Not reached	67	48
Seligson et al. [17]	12	CdA + ARA-C + IDA	NR	NR	NR	42	NR
Kadia et al. [18]	118	CdA + LDAC/ Decitabine	13.8	10.8	NR	58	23

pts: patients; OS: overall survival; DFS: disease free survival; EFS: event free survival; CR: complete remission; CLIA: cladribine, idarubicin, Ara-C; CdA: cladribine; Ara-C: aracytin; IDA: idarubicin; DAC: daunorubicin, Ara-C, CdA; IAC:IDA, Ara-C, CdA; CLAG-M: CdA, ara-C, filgrastim, mitoxantrone; LDAC: low dose Ara-C; NR:not reported.

rate of 58%. Median DFS and OS were 10.8 and 13.8 months, respectively and 18 (23%) patients (median age 64 years), went on to receive HSCT. The regimen was well tolerated, with one (1%) death within the first 4 weeks and eight (7%) deaths within the first 8 weeks. Based on these positive results, a phase II study (NCT03586609) including an induction phase based on venetoclax added to CdA plus LDAC followed by consolidation with CdA plus LDAC alternating with 5-Azacitidine (5-AZA) with venetoclax in elderly patients with untreated AML is ongoing. A summary of published data for CdA in de novo adult AML is presented in Table 3.

Safety

The immunosuppressive effects of CdA are profound and prolonged. Lymphocyte counts may decrease by 50% after 7 days of treatment, with a universal decrease in CD4 cells and reductions in CD8 cells in almost all cases [59,60]. The clinical importance of this immunosuppression is the frequency of infections, particularly with opportunistic pathogens, even in the absence of neutropenia or concurrent corticosteroids. However, despite the prolonged reduction in CD4 cells, response to CdA therapy is characterized by an improvement in various mononuclear cells and other immune functions, which may explain why opportunistic infections tend to occur early during therapy [61]. Opportunistic infections as herpes simplex, pneumocystis, toxoplasmosis, herpes zoster, cytomegalovirus, and disseminated fungal, have been reported in up to 26% of treated patients in the absence of anti-infective prophylaxis [59]. The PALG compared infectious complications following DAC and DA induction in AML patients [62] reporting that the addition of CdA to DA did not prolong neutropenia (days with ANC $<1000/\mu L$: 18 days with DAC, 19 days with DA) and did not increase the incidence of fever related to infection, fever of unknown origin, or grade 3/4 documented infections [62]. Moreover, no differences in pathogen distribution or infection related mortality were reported. However, in MDACC study [18] including 118 elderly AML patients, there were 88 documented infectious events of grade 3 or worse, nine (10%) of which resulted in deaths during the study.

Cladribine has also been associated with neurotoxicity which may be related to continuous exposure to the drug at high serum levels. Vahdat et al. reported that among 36 patients treated with CdA (doses ranging from 5 to 21 mg/m^2/day) for 5 days, sensorimotor peripheral neuropathy, characterized by axonal degeneration and secondary demyelination, occurred in 40% of patients treated at the 19 mg/m^2 dose level and in 100% treated at the 21 mg/m^2 dose level [41]. Patients developed symptoms between 4 and 7 weeks after CdA initiation and 80% of them had at least partial neurologic improvement between 8 and 10 weeks after the end of therapy. Therefore, CdA shares with fludarabine, the delayed occurrence of neurotoxicity generally reported 3–6 weeks after completion of therapy. However, less severe neurologic side effects have been described when standard doses of CdA (5 mg/m^2/day) have been administered and grade 3–4 neurotoxicity remains uncommon with all currently used dosing regimens.

An additional adverse effect of CdA is the risk of secondary malignancies. Therapy-related MDS has been reported in at least 1.6% of CdA treated patients [63]. Hassan et al. cited a mean onset of 4.3 years from the time following completion of CdA to the diagnosis of AML [64]. Unfortunately, most patients with

treatment-resistant AML will not live long enough to develop secondary cancers.

Discussion and future perspectives

Cladribine has been shown to have significant anti-leukemic activity in patients with AML. Although trials with single agent CdA showed disappointing results in this setting, CdA combined with agents such as anthracyclines and ARA-C, appears to improve the efficacy of such regimens and represents an effective option for patients with AML. An important property of CdA is to amplify the bioactivation of ARA-C. It is reported that pretreatment with CdA increased the rate of Ara-CTP accumulation in leukemic blasts by 50–65% *in vitro* and *in vivo* pharmacological studies, and the addition of G-CSF may further improve the effects of CdA in combination with ARA-C [8,40].

In recent updates of the AML NCCN guidelines, the use of CdA in combination with the DA regimen (7 + 3 + 5 DAC) for patients less than 60 years of age has been changed from a category 1 recommendation to category 2 A [19]. The addition of CdA for 5 days to the 7 + 3 DA regimen was added to the NCCN guidelines based on data from 2 phase III Polish studies [15,16] that reported that the 7 + 3 + 5 DAC regimen exhibited increased CR rates and overall survival, particularly in high-risk AML subtypes [52]. Although these results are promising, questions of the external validity and applicability of this study to patients and practice in the US have been raised, with both studies showing surprisingly high response rates compared with similarly designed studies published at that time [48–51]. However, the retrospective findings of Jaglal et al. [56] showing improved outcomes with CLAG-M versus 7 + 3 in patients with secondary AML after prior hypomethylator therapy are encouraging and warrant further randomized studies. Furthermore, results from several studies [18,52,65] have shown high remission rates with improved survival among patients with *NPM1* and *FLT3-ITD* mutations treated with CdA combination regimens. Therefore, it might be useful to investigate whether combinations of cladribine-based regimens and FLT3 inhibitors improve the outcome of *FLT3-ITD*+ AML.

The role of CdA combination regimens such as DAC in de novo AML remains controversial. Table 4 summarizes the ongoing clinical trials that incorporate CdA in remission induction of AML.

The Polish group also assessed the efficacy of DA and DAC regimens as frontline approaches in patients older than 60 years showing no difference in CR at first induction [58]. However, in this setting promising results have been reported by MDACC group [18] that reported as a regimen including CdA plus low-dose ARA-C alternating with decitabine might have superior response rates (58% vs 25–31% in 5-AZA studies vs 24–26% in decitabine studies vs 7–11% in LDAC studies), better long-term survival (median OS 13.8 months vs 7.7–9.4 months in 5-AZA studies vs 5.5–7.7 months in decitabine studies vs 5–6.2 months in LDAC studies), and good tolerability compared with previous evidence of treatment with hypomethylating agents [66–69] and LDAC [70,71]. Therefore, this therapeutic strategy seems to be effective and tolerable in elderly or unfit people with AML, and a new trial is ongoing with the purpose to further improve response rates and outcomes adding venetoclax to this regimen.

Several studies [11,12,45,46] have also confirmed the effectiveness of cladribine-based treatment protocols in R/R AML; the combined schedule of CLAG showed much significantly higher efficacy than CdA monotherapy in CR rate in this setting. A recent meta-analysis [45] observed that nearly half of the R/R AML patients responded to cladribine-based treatments, which demonstrated that cladribine-based therapies

Table 4. Ongoing clinical trials including cladribine in induction treatment of AML.

Clinical trial identifier	Phase	Summary
NCT02096055	2	A MDACC trial to examine CdA in combination with HiDAC 1.5–2 g/m^2/day, and IDA in adults with AML, high-risk MDS, and CML with blast crisis
NCT01515527	2	A MDACC trial to examine CDa plus LDAC alternating with decitabine in patients with AML or high-risk MDS
NCT03586609	2	A MDACC trial to examine venetoclax, CdA, LDAC, and 5-AZA in treating patients with previously untreated AML
NCT02096055	2	A MDACC randomized trial including 4 arms in induction of elderly patients with AML: single-agent SGI-110 for 5 days (Arm A) or 10 days (Arm B) or combined with IDA (Arm C) or CdA (Arm D)
NCT03257241	3	A PALG prospective trial to compare the efficacy of two standard induction therapies (DA-90 vs DAC) and two standard salvage regimens (FLAG-IDA vs CLAG-M) in AML patients $\leq$ 60 years old (PALG-AML1/2016)
NCT03012672	3	A Fred Hutchinson trial to compare higher and lower doses of CLAG-M in induction of less-fit adult patients with AML
NCT02323022	3	A Chinese randomized trial to compare IAC regimen with IA-10 and IA-12 in the induction of newly diagnosed AML

CdA: cladribine; HiDAC: high dose aracytin; IDA: idarubicin; LDAC: low dose aracytin; AML: acute myeloid leukemia; MDS: myelodysplastic syndrome; 5-AZA: 5-azacitidine; DA-90: daunorubicin 90 mg/m^2 plus aracytin; DAC: daunorubicin, aracytin, Cda; FLAG-IDA: fludarabine, aracytin, filgastrim, IDA; CLAG-M: CdA, aracytin, filgastrim, mitoxantrone; IA-10: IDA 10 mg/m^2, aracytin; IA-12: IDA 12 mg/m^2, aracytin; 3CML: chronic myeloid leukemia.

are effective in R/R AML with an overall CR rate of 42.2% and ORR rate of 49.7%. However, numerous publications have also described the use of fludarabine combination regimens for R/R AML, the most popular of which is the FLAG ± Ida (fludarabine, ARA-C, filgrastim, and idarubicin) regimen [72–74]. This regimen has not been directly compared with CLAG in any published trial and, at the current time, it is unknown which purine analog, fludarabine or CdA, is the preferred agent in R/R AML. Nevertheless, the use of cladribine-based combined therapy in R/R AML is strongly recommended being a valid option as a bridge to transplant in younger patients who achieve CR and holding a relatively safe toxicity profile.

Conclusions

Cladribine-based combination treatments may be an effective induction regimen for younger de novo AML with high rates of CR, but further randomized studies are needed to demonstrate better results of these therapies compared with standard 7 + 3 and to assess the potential benefit of CdA combined with new targeted molecules. In elderly or unfit patients with newly diagnosed AML, the combination of CdA and LDAC alternating with decitabine appears to be a safe and highly effective treatment and further testing of this regimen is warranted, and could help to provide a new, effective option for reduced-intensity therapy in this population. Cladribine combination regimens are also effective in R/R AML patients producing CR in nearly half of the patients.

Disclosure statement

No potential conflict of interest was reported by the authors.

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