Clofarabine in the treatment of acute myeloid leukemia in older adults

Ther Adv Hematol
(2013) 4(1) 5–13
DOI: 10.1177/2040620712461666

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Abstract:
Objective: To review the literature evaluating the efficacy and tolerability of clofarabine as a single agent and in combination therapy for older patients with acute myeloid leukemia (AML).
Method: A literature search of the PubMed database (1996–April 2012) using the search terms clofarabine and acute myeloid leukemia was performed. All relevant English language articles were reviewed. Clinical trials with patients aged 50 years or older diagnosed with AML were included.
Results: Two studies evaluating clofarabine as monotherapy and five studies evaluating clofarabine in combination with cytarabine were reviewed. Clofarabine demonstrated activity in older adults with AML. Response rates and median overall survival (OS) for patients receiving clofarabine were similar to those for patients receiving conventional induction chemotherapy. The induction mortality rate with clofarabine was lower than that seen with intensive chemotherapy. However, clofarabine was associated with a significant risk of severe complications including myelosuppression and sepsis.
Conclusion: Clofarabine is an active agent for the treatment of older patients with AML as a single agent or in combination therapy. Based on published data and side-effect profiles, clofarabine may be an appropriate alternative to intensive chemotherapy for older patients with AML, offering similar response rates to traditional 7+3 chemotherapy with potentially decreased induction mortality. The use of clofarabine in combination with newer agents including DNA methyltransferase inhibitors like decitabine is a promising approach for older patients who are not eligible for intensive chemotherapy. Additional randomized controlled trials are needed to directly compare the efficacy of clofarabine as a single agent and in combination therapy compared with intensive chemotherapy regimens.

Keywords: acute myeloid leukemia, clofarabine, older adults

Acute myeloid leukemia in older adults

Acute myeloid leukemia (AML) is a heterogeneous disorder resulting from both genetic and epigenetic alterations leading to abnormal differentiation and dysregulated proliferation of hematopoietic progenitors. The incidence of AML increases with advanced age. At age 40 years, there is only 1 case of AML per 100,000. This increases to 15 per 100,000 at age greater than 75 years. The median age at diagnosis is 65 years. Clinical outcomes for older patients being treated with conventional intensive chemotherapy regimens remain poor compared with younger patients [Erba, 2007]. AML of older adults is a different disease than that seen in younger individuals. Older patients with AML tend to present with lower white blood cell counts and peripheral blast cell percentages. They are also more likely to have a secondary AML, rather than a *de novo* AML, that is frequently resistant to chemotherapy. Poor performance status (PS) and comorbid medical illnesses also pertain to a worse tolerance of chemotherapy and outcome for older patients. Newer treatment options are needed for this population that are effective and less toxic then conventional intensive chemotherapy [Leith *et al.* 1997].

An important predictor of outcome for patients with AML following induction and consolidation

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therapy depends on the patient's cytogenetic profile. This refers to a karyotypic evaluation of the leukemic blasts that stratifies patients as having favorable, intermediate, or unfavorable risk disease. These groupings thus predict the likelihood of complete remission (CR) and overall survival (OS) in individual patients. It also provides prognostic information for guiding therapeutic choices, particularly regarding consolidation therapy [Griffiths, 2007]. The poor cytogenetic abnormalities associated with treatment failure in young patients including deletional abnormalities of chromosome 5,7 or complex karyotypes are seen more frequently in older patients. Compared with young patients, older patients with AML are also more likely to have primary multidrug-resistant disease as well as secondary AML. These differences between AML in older compared with younger patients contribute to the poorer response rate to treatment seen in this group. It also suggests a difference in the biological characteristics of AML in older patients.

The treatment of AML includes both induction and consolidation chemotherapy. The overall goal of induction is to provide CR (< 5% blast cells in the bone marrow, absolute neutrophils count > 1000/μl and platelet count > 100,000/μl). Consolidation therapy is then given to help maintain a durable remission. A common intensive induction chemotherapy regimen referred to as 7+3 consists of 7 days of intravenous cytarabine (100–200 mg/m^2/day) in combination with 3 days of an anthracycline (usually daunorubicin 45–60 mg/m^2/day or idarubicin 12 mg/m^2/day). Standard induction therapy with 7+3 in older patients has resulted in CR rates ranging from 30% to 50% and induction mortality rates of 10–35%. Remissions are usually transient and rarely last more than 12 months. The median time to treatment death is 5–10 months; with less than 10% of patients remaining in remission at 3 years. The advisability of intensive chemotherapy in patients with AML is dependent on a patient's leukemia cytogenetics, age, PS, and other comorbidities. The National Comprehensive Cancer Network guidelines list clofarabine as an alternative to intensive 7+3 chemotherapy. It categorizes clofarabine as an intermediate-intensity therapy and hypomethylating agents (e.g. azacitidine and decitabine) as low-intensity therapies. Treatment decisions for older patients with AML require careful attention to the risk and potential benefits of treatment when risk stratifying patients.

Clofarabine pharmacology

Clofarabine is a second-generation purine nucleoside analogue designed to overcome the limitations and to incorporate the best qualities of both cladribine and fludarabine. Clofarabine enters cells by passive transport across lipid membranes as well as by active nucleoside transport. Once inside the cell, clofarabine is phosphorylated to its active triphosphate form by cellular kinases, including deoxycytidine kinase. Whereas fludarabine and cladribine inhibit only DNA polymerase and ribonucleotide reductase, respectively, clofarabine inhibits both of these enzymes [Kantargian *et al.* 2003, Tran and Yang, 2012]. This results in depletion of the amount of deoxynucleotide triphosphate available for DNA replication, as well as inhibition of DNA strand elongation and RNA transcription [Faderl *et al.* 2006]. Given its mechanisms of action, clofarabine was predicted to work synergistically with other chemotherapeutic agents such as other purine nucleoside analogues and DNA-damaging or cross-linking agents such as anthracyclines and platinum agents. It initially showed efficacy in treating pediatric acute lymphoblastic leukemias and gained approval from the US Food and Drug Administration in 2004 [Kantarjian *et al.* 2007]. Since that time clofarabine has been studied as a single agent and in combination therapy for the treatment of older patients with AML.

Clinical trials

A search of the PubMed and Ovid databases using the terms clofarabine and acute myeloid leukemia was completed. All relevant English language articles published from 1996 to April 2012 were reviewed. Clinical trials with patients with AML who were 50 years of age and older were included. Two studies looking at clofarabine as monotherapy and five studies looking at its use as combination therapy are discussed here (Table 1).

Clofarabine monotherapy

The results of two consecutive phase II studies (UWCM-001 and BIOV-121) were reported by Burnett and colleagues [Burnett *et al.* 2010]. Both studies recruited untreated older patients with AML to receive up to four or six 5-day courses of clofarabine. Patients in UWCM-001 were either older than 70 years or 60–69 years of age with poor PS [World Health Organization (WHO) PS > 2] or with cardiac comorbidity.

Table 1. Clinical responses to clofarabine monotherapy and clofarabine in combination with cytarabine

Reference	AML study population	Patients, *N*	Age range (median)	ORR (CR + CRp), %	Complete remission, %	Overall survival (weeks), median	Induction morality, %
Monotherapy							
Burnett *et al*. [2010]	Untreated	106	60–84 (71)	48	32	19	18
Kantarjian *et al*. [2010]	Untreated	112	60–88 (71)	46	38	41	9.8
Combination therapy							
Faderl *et al*. [2005]	Relapsed/ refractory	32	18–84 (63)	38	24	22	7
Faderl *et al*. [2006]	Untreated	60	50–74 (61)	60	52	41	6.6
Faderl *et al*. [2008b]	Untreated	70	60–83 (71)	56	63	45	19
Agura *et al*. [2011]	Relapsed/ refractory Untreated	30	38–82 (67)	53	47	24	20
Faderl *et al*. [2012]	Untreated	60	60–81 (69)	66	58	24	7

AML, acute myeloid leukemia; ORR, overall response rate; CR, complete remission; CRp, complete recovery of platelets.

Patients in BIOV-121 were older than 65 years and deemed unsuitable for intensive chemotherapy [Burnett *et al.* 2010]. Eligible patients were required to have adequate renal and hepatic function. Intravenous clofarabine was administered at 30 mg/m^2 over 1 h daily on days 1–5 of each course. For patients with response to treatment or stability of disease, courses were repeated every 28 days for a maximum of four (UWCM-001) or six cycles (BIOV-121). The maximum daily dose of clofarabine was reduced to 20 mg/m^2 in both studies due to grade 4 hematologic toxicities [Tran and Yang, 2012].

The combined studies included a total of 106 patients (40 in UWCM-001, 66 in BIOV-121), with a median age of 71 years. Thirty percent of patients had adverse cytogenetics, 36% had a WHO PS of 2 or greater, and 16% had secondary AML (Burnett *et al.* 2010). The mean number of courses administered was 1.6. The overall response rate (ORR), which included CR and CRi (remission with incomplete recovery of peripheral blood counts), was 48% (Table 1). Over 30% of patients with secondary AML or adverse cytogenetics achieved either a CR or CRi. The median OS was 19 weeks, which was increased to 47 weeks among patients who achieved a CR. Twelve-month OS was 10% with only one course of clofarabine *versus* 50% for patients who received at least two courses. The 30-day mortality rate was 18%, with sepsis being the most common cause of death [Burnett *et al.* 2010].

The results of both UWCM-001 and BIOV-121 studies confirmed the efficacy of clofarabine in the treatment of older patients. Treatment was well tolerated with elevated liver function test, mucositis, and myelosuppression being the most common side effects. These were minimized by reducing the dose to 20 mg/m^2. Clofarabine showed improved CR compared with historical controls using low-dose cytarabine (LDAC). The rate of CR/CRi with clofarabine was significantly superior to that of LDAC (48% *versus* 17%). The authors also noted that CR with clofarabine occurred at a similar rate in patients with adverse cytogenetics (44%) as in the intermediate group (54%). For patients with secondary AML, the response rate was 31% for clofarabine compared with 4% with LDAC [Burnett *et al.* 2010]. These studies confirm the activity and tolerability of clofarabine as monotherapy in older patients with AML.

In 2010 Kantarjian and colleagues completed 'Classic II', a phase II study of clofarabine monotherapy in previously untreated older patients with AML and unfavorable prognostic factors. Patients were required to be older than 60 years and have at least one unfavorable prognostic factor [i.e. antecedent hematologic disorder, intermediate or advanced cytogenetics, Eastern Cooperative Oncology Group (ECOG) PS of 2, age over 70 years]. Patients were required to have adequate renal, hepatic and cardiac function. The induction dose of clofarabine was 30 mg/m^2 daily for 5 days. One cycle of reinduction chemotherapy was allowed for patients with persistent

disease and without evidence of progression. Patients who achieved a CR or a remission without complete recovery of platelets (CRp) then received consolidation chemotherapy with clofarabine at 20 mg/m^2 daily for 5 days. Patients received the same dose for both reinduction and consolidation. A total of six cycles of clofarabine were permitted [Kantarjian *et al*. 2010].

A total of 112 patients, with a median age of 71 years, were included in the study. A total of 78% of patients had at least two unfavorable prognostic factors. The median number of administered cycles was two. A total of 34% of patients required reinduction, and 25% received at least one cycle of consolidation [Tran and Yang, 2012]. The ORR, consisting of CR and CRp, was 46%, including over 40% of patients with secondary AML or adverse cytogenetics achieving a CR or CRp. The median disease-free survival (DFS) was 37 weeks (Table 1). The ORR and the DFS did not seem to be significantly affected by number of unfavorable prognostic factors present. The median OS was 41 weeks. For patients who achieved a CR the OS was increased to 72 weeks [Kantarjian *et al*. 2010]. For most patients the regimen was well tolerated with only 6% of patients having to discontinue treatment due to adverse events, including prolonged myelosuppression with 46% of patients developing grade 4 neutropenia. The 30-day mortality rate was 9.8% [Tran and Yang, 2012; Kantarjian *et al*. 2010].

The authors of this study reported that single-agent clofarabine compared favorably with outcomes of 7+3 induction therapy in older patients with AML. They noted that other studies in unselected older patients with AML treated with 7+3 resulted in a median DFS of 7–11 months for patients older than 56 years. The DFS rate for selected older patients with AML with unfavorable prognostic factors is expected to be worse. However, this study revealed a median OS of 10 months for this selected group, which is similar to the results seen in studies of unselected older patients with AML [Kantarjian *et al*. 2010]. This study confirmed clofarabine's efficacy and acceptable toxicities with low mortality in older patients with AML with unfavorable prognostic factors.

Clofarabine in combination with cytarabine

The benefit of combining clofarabine with cytarabine, a pyrimidine nucleoside analogue, was hypothesized given *in vitro* data showing increased conversion of cytarabine to its active triphosphate form via deoxycytidine kinase when cytarabine was given after clofarabine. In 2005 Faderl and colleagues published a phase II study of clofarabine in combination with cytarabine (Ara-C) to treat patients with relapsed and refractory AML. Patients were required to be 50 years or older. They were also required to have an ECOG PS of 2 or less and no favorable cytogenetics. Patients were treated with intravenous cytarabine 1 g/m^2 daily on days 1–5 and clofarabine 40 mg/m^2 daily given 4 h after clofarabine on days 2–5 and clofarabine alone on day 6. The study allowed up to two reinduction cycles, as well as six consolidation cycles for responding patients [Faderl *et al.* 2005].

A total of 60 patients were enrolled with a median age of 61 years and 30% of patients had adverse cytogenetics or MDS-related secondary AML. The median number of cycles received was 2, with 20% of patients receiving 1 reinduction cycle, and 81% receiving at least 1 cycle of consolidation . The ORR for the study was 60%. A CR or CRp was reported for more than 30% of patients with adverse cytogenetics or myelodysplastic syndrome (MDS)-related secondary AML. The median OS was 10.3 months, which increased to 23.5 months for those with CR (Table 1). A 7% mortality rate was reported during the first induction course with sepsis being the most common cause of death [Faderl *et al.* 2005; Griffiths, 2007].

This study examined the efficacy and tolerability of combination therapy with clofarabine with Ara-C in older patients with relapsed or refractory AML. In its active from, clofarabine triphosphate is accumulated and retained in leukemia blast. As a result there is impaired DNA replication, as well as inhibition of DNA strand elongation and RNA transcription which makes the cell increasingly vulnerable to other nucleoside analogues like Ara-C. This synergistic effect was further tested in clinical studies.

In 2006 Faderl and colleagues published a study on the use of clofarabine and cytarabine combination as initial induction therapy for newly diagnosed AML in patients 50 years of age or older. The study enrolled 60 patients with newly diagnosed AML or high-risk MDS. Eligibility criteria also included ECOG PS of 2 or bellow, with adequate liver and renal function with either intermediate or poor risk cytogenetics. The treatment schedule included induction therapy with intravenous clofarabine 40 mg/m^2 daily for 5 consecutive

days on days 2–6 followed 4 h later by cytarabine at a dose of 1 g/m^2 daily on days 1–5. On day 1, only cytarabine was administered, and on day 6, only clofarabine was given. Cycles were repeated every 4–6 weeks depending or response. Patients were able to receive up to three induction cycles or treatment until CR. Responding patients were able to receive up to six additional courses of maintenance therapy as consolidation with a clofarabine dose of 40 mg/m^2 daily for 3 days followed 4 h later by cytarabine at 1 g/m^2 daily for 3 days [Faderl *et al.* 2006].

This phase II study looked at 60 patients with newly diagnosed AML with a median age of 61 years. The study enrolled patients with intermediate or poor risk cytogenetics. This included 50% of patients with abnormal karyotypes with monosomy 5, monosomy 7, or inversion 17. A total of 21% of patients were noted to be FMS-like tyrosine kinase 3 (FLT3) positive and 48% of patients had secondary AML [Faderl *et al.* 2006].

The combination of clofarabine and cytarabine as front-line induction therapy for older patients with AML appeared to be well tolerated. The most frequent grade 1 or 2 side effects included diarrhea, nausea, vomiting, headaches, and liver function abnormalities. Myelosuppression was a common effect of treatment and resulted in 43% of patients developing neutropenia and 33% developing septicemia. The study reported four deaths with induction therapy. This regimen was active and resulted in an ORR of 60% with 52% CR and 8% CRp (Table 1). The median OS was 10.3 months, however for patients who had a CR the OS increased to 23.5 months [Faderl *et al.* 2006]. This study showed that clofarabine combination has activity with good CR rate and an acceptable safety profile. However, remission duration and OS did not appear to be improved compared with other induction regimens like 7+3.

The question of optimal dosing of clofarabine and cytarabine was investigated by Faderl and colleagues in 2008 with a randomized study looking at clofarabine with LDAC as front-line therapy for older patients with AML. The study treated 70 patients with newly diagnosed AML who were randomized to treatment with clofarabine alone *versus* clofarabine plus LDAC. All patients were greater than 60 years old with a median age of 71. They all shared either intermediate or poor cytogenetics. The combination arm of the study had more patients with secondary AML and FLT3-positive AML then the clofarabine alone arm [Faderl *et al.* 2008a, 2008b].

The study patients received induction therapy with intravenous clofarabine 30 mg/m^2 daily for 5 days with or without subcutaneous cytarabine 20 mg/m^2 daily for 14 days. This induction therapy was followed by consolidation with clofarabine daily for 3 days with or without 7 days of cytarabine. Sixteen patients received clofarabine alone and 54 the combination. The treatment was fairly well tolerated, with the most nonhematologic adverse effect being elevated liver studies. Acute renal failure requiring hemodialysis occurred in 19% of patients treated with clofarabine alone and in 15% of patients on combination therapy. Nearly all patients experienced grade 3 myelosuppression. Sepsis was noted in 38% of patients on clofarabine only and in 30% of those in the combination arm [Faderl *et al.* 2008b].

Overall, 56% of patients achieved a CR. However, the proportion achieving CR was significantly higher in the combination arm (63% *versus* 31%). Interestingly, induction mortality was 19% in the combination arm *versus* 31% in the clofarabine alone arm (Table 1). The authors noted that the difference in induction mortality between the two arms of the study was not statistically significant. They also suggest that differences in pretreatment characteristics between the groups as well as randomization issues in the study may offer an explanation for the differences in mortality. The study demonstrated a better event-free survival favoring the combination arm (7.1 months *versus* 1.7 months). In addition, a nonsignificant OS benefit was seen in the combination arm (11.4 months *versus* 5.8 months). A statistically significant median event-free survival of 7.1 months was noted for patients on combination therapy *versus* 1.7 months for those on clofarabine alone. This study demonstrated that combination therapy with LDAC is effective in improving event-free survival without known OS benefits [Faderl *et al.* 2008b]. The efficacy and safety of clofarabine in combination with cytarabine in *de novo* and relapsed or refractory disease in older patients with AML at high risk of anthracycline toxicity was evaluated by Agura and colleagues in their phase II study published in 2011. In this study high-risk patients were defined as having a history of cardiovascular disease, including myocardial infarction or stenting [Agura *et al.* 2011]. Thirty patients with a median age of 67 were

treated with clofarabine 40 mg/m^2 for 5 days followed 4 h later by Ara-C 1000 mg/m^2. The study looked at a heavily pretreated population. Approximately two-thirds of patients received prior lines of treatment with the most common treatment being 7+3. Three patients had undergone prior autologous hematopoietic stem cell transplantation (HSCT) and one patient had received a previous nonmyeloblative allogeneic HSCT. Cardiovascular history including MI, bypass and cardiomyopathy was noted in 37% of patients. Patient cytogenetics included both intermediate and unfavorable groups [Agura *et al*. 2011].

The ORR of therapy in this population was 53% with 47% of patients receiving a CR. Half of the patients who received a CR were able to proceed to HSCT. This response rate was observed in all cytogenetic risk groups. The median disease free survival was 9.5 months with a median OS of 6months. The toxicities of this regiment where similar to those noted in prior studies. Grade 3 myelosuppression and grade 4 neutropenia were observed in all patients. Other side effects included diarrhea, skin rash, mucosites and elevated transaminases. Cardiac toxicities were limited to atrial fibrillation which was transient and reversible. The 30 day mortality rate in this study was 20% with septicemia and multiorgan failure occurring in 13% of patients. This study demonstrated the efficacy of combination clofarabine plus Ara-C in a heavily pretreated population with cardiac risk factors.

With the development of novel agents such as 5-azacytidine and decitabine, newer treatment strategies are being tested to find more effective and less toxic treatments. Decitabine is a cytosine analog with clinical activity in myelodysplastic syndromes (MDS) and other myeloid leukemias. The drug works by inducing DNA hypomethylation. DNA hypomethylation is an epigenetic modification of DNA that has a role in controlling gene expression [Garcia-Manero *et al*. 2006]. In 2012 Faderl and colleagues published their results looking at the addition of alternating doses of decitabine with LDAC as consolidation therapy for older patients with AML. This study attempted to deliver lower doses of clofarabine over a longer duration of therapy. It also used multiple drugs with different mechanisms of action to prevent cross resistance [Faderl *et al*. 2012].

In the study 60 patients over the age of 60 where treated with combination clofarabine and LDAC induction therapy followed by a prolonged consolidation regimen alternating between cytarabine and decitabine. The induction regimen included clofarabine at 20 mg/m^2 for 5 days in addition to subcutaneous cytarabine at 20 mg/m^2 twice a day for 10 days. Patients who had a CR were then treated with consolidation treatment with repeated courses of clofarabine 20 mg/m^2 for 3 days plus subcutaneous cytarabine 20 mg/m^2 twice daily for 7 days, alternating with decitabine 20 mg/m^2 for 5 days. Each cycle was repeated every 4–7 weeks depending on the patient's blood counts for a total of 17 cycles. The patient population consisted of 23% with secondary AML or an antecedent hematologic disorder and 33% with complex cytogenetics.

The goals of this study were to decrease induction mortality by attenuating the induction dosing while extending the post-remission therapy. The final goal was to include a third drug in the treatment that is not cross resistant and might circumvent build up of drug resistance to the two-drug combination. The study achieved its first two goals but its third goal has not yet been clearly demonstrated [Kantarjian *et al*. 2010]. The results were compared with a historic group of patients treated only with clofarabine and cytarabine. Compared with the historic control, the response rate appeared identical; however, induction mortality was higher in the historical group. There did not appear to be a difference in relapse-free survival or OS between the two groups. The results showed an ORR of 66% with 58% CR, and 5% CRp (Table 1). The results also showed a relapse-free survival of 14.1 months and a median survival of 24.2 months, with an 8-week mortality of 7% [Faderl *et al*. 2012]. Clofarabine plus LDAC alternating with decitabine appears to be an active and safe induction regimen for older patients with AML. However, an OS benefit with prolonged consolidation remains unproven.

The decreased mortality and tolerability seen with induction clofarabine has also been seen with its use in consolidation therapy. A recent *post hoc* analysis of the Classic II study by Claxton and colleagues examined outpatient administration of clofarabine in older patients with AML. The study enrolled 112 patients treated with induction clofarabine at a dosage of 30 mg/m^2 daily for 5 days.

Following induction, patients received consolidation clofarabine at 20 mg/m^2 daily for 5 days, given every 28 days. In this study 28 patients received a combined total of 85 cycles of clofarabine as consolidation. A total of 58 of those cycles or 68.2% were administered in an outpatient setting. The analysis revealed that patients treated both in the inpatient and outpatient setting had similar rates of adverse events. The most common adverse events included nausea and febrile neutropenia. Febrile neutropenia was noted in 50% of patients receiving induction therapy. Infections are a significant concern for patients treated with clofarabine [Claxton *et al.* 2012]. However, prophylactic antibiotic therapy has been used successfully in the treatment of outpatient s receiving consolidation clofarabine. The risk of infection and gastrointestinal toxicities related to clofarabine requires close monitoring. In appropriately selected patients it can be well tolerated in the outpatient setting.

Discussion

Treatment of older patients with AML remains a significant challenge. The outcome of older patients with AML has not improved in the last three decades (Erba, 2007). This likely reflects a worse biology in older patients with AML in addition to decreased tolerability of treatment. The use of standard induction therapy with 7+3 chemotherapy has been reported to have CR rates as low as 30%, with induction mortality rates as high as 35% for patients over the age of 70. Remissions are usually transient in this age group. Newer agents and strategies are needed to treat these challenging patients. A review of the literature has demonstrated clofarabine's activity as a single agent and in combination therapy for the treatment of older patients with AML.

The initial studies looking at clofarabine as a single agent in treating older patients with AML by Burnett and colleagues (UWCM-001 and BIOV-121) demonstrated an ORR of 48% with an induction mortality of 18% [Burnett *et al.* 2010]. These findings were verified by Kantarjian and colleagues in the 'Classic II' trial examining clofarabine for treating older patients with AML with poor prognostic factors, including poor risk cytogenetics [Kantarjian *et al.* 2010]. The ORR in this study was 46% with an induction mortality of 9.8%. ORRs were further improved by combining clofarabine with cytarabine, as demonstrated by Faderl and colleagues in their study published in 2005 [Faderl *et al.* 2005]. The combination regimen proved to be well tolerated and effective, with an ORR of 60% and an induction mortality of 7%. Further studies by Faderl confirmed the efficacy of combination therapy with an ORR of 60% and an induction mortality of 6.6% [Faderl *et al.* 2006]. Various dosing regimens have been studied to improve tolerance, including the use of LDAC and clofarabine. The study by Faderl and colleagues in 2008 revealed an ORR of 56% and a 19% induction mortality rate when using the combination of LDAC and clofarabine [Faderl *et al.* 2008b]. The safety of clofarabine in patients not eligible for anthracyclines was shown by Agura and colleagues who looked at combination therapy for patients with extensive cardiovascular risk factors [Agura *et al.* 2011]. The ORR of this study was 53%, including half of those patients going on to stem cell transplant. However, the induction mortality in this trial was 20%, with sepsis being the most common cause of death. The addition of novel agents such as 5-azacytidine and decitabine to current treatment strategies is now being evaluated in an effort to provide a more effective and less toxic therapy. The most recent study from Faderl and colleagues looked at clofarabine plus LDAC alternating with decitabine as frontline therapy for older patients with AML resulted in an ORR of 66% and an induction mortality of 7% [Faderl *et al.* 2012].

The studies reviewed here demonstrated the efficacy and tolerability of clofarabine as both a single agent and in combination with cytarabine. Combination therapy resulted in ORRs ranging from 38% to 66% and CRs ranging from 24% to 63%. These findings were seen even in patients with adverse cytogenetics. OS with clofarabine appears to be similar to that seen with standard 7+3 regimens. However, these studies did suggest a modest improvement in induction mortality compared with standard 7+3. Induction mortality for older patients with standard chemotherapy can range from 10% to 35%. With clofarabine plus LDAC, the 8-week mortality rate was as low as 7% (Federl *et al.* 2005). In the trials reviewed here the induction mortality rate ranged from 7% to 20%, with sepsis being the most frequent cause of death. These trials suggest an improved tolerance by altering the dosing of cytarabine in addition to improved efficacy with the addition of novel agents. The addition of clofarabine to agents such as decitabine provides a promising approach for better tolerated and more effective regimens for the treatment of older patients with AML. The

use of these agents in the outpatient setting also offers the potential for cost savings relative to standard cytotoxic induction chemotherapy. The studies presented here highlight the potential benefit of clofarabine as offering a slight improvement in induction mortality over 7+3 for older patients with AML. However, this small series of studies is likely not adequate to conclude that clofarabine is superior to 7+3 but further investigation is warranted.

Conclusion

Compared with intensive chemotherapy regimens, clofarabine is associated with similar efficacy and potentially lower induction mortality for older patients with AML. As such, it may be an appropriate alternative treatment option for older patients with decreased PS or those who are unable to tolerate an anthracycline. Dosing and scheduling modifications of clofarabine plus cytarabine with the addition of novel agents warrants further evaluation in the treatment of older patients with AML.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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