NHS England

Evidence review: Clofarabine as a treatment for refractory or relapsed acute myeloid leukaemia with intent to bridge to stem cell transplantation
Evidence review:
Intervention: Clofarabine
Indication: Treatment of refractory or relapsed acute myeloid leukaemia (AML) with intent to bridge to stem cell transplantation

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1. Introduction

The technology clofarabine (Evoltra, Sanofi) is a purine nucleoside anti-metabolite (1). Its anti-tumour activity is believed to be due to three mechanisms:

- DNA polymerase α inhibition resulting in termination of DNA chain elongation and/or DNA synthesis/repair.
- Ribonucleotide reductase inhibition with reduction of cellular deoxynucleotide triphosphate (dNTP) pools.
- Disruption of mitochondrial membrane integrity with release of cytochrome C and other proapoptotic factors leading to programmed cell death even in non-dividing lymphocytes (1).

It is licensed to treat acute lymphoblastic leukaemia in paediatric patients (≥ 1 year old) who have relapsed, or are refractory, after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response (1). The recommended dose in monotherapy is 52mg/m$^2$ of body surface area given by intravenous infusion over two hours daily for five consecutive days.

Clofarabine is used in the UK (via CDF funding) for treating patients with refractory or relapsed acute myeloid leukaemia (AML), with intent to use treatment to bridge to bone marrow transplant (2). The CDF received an estimated 56 applications for clofarabine to treat refractory or relapsed AML in 2014/15 (3).

Acute myeloid leukaemia

AML is a malignant disease of bone marrow in which precursors of blood cells are arrested in an early stage of development (4). Symptoms may be related to bone marrow failure (causing anaemia, neutropenia and thrombocytopenia) or organ infiltration (usually liver or spleen) (4). Fever is a common presenting sign, and symptoms include fatigue, dizziness, shortness of breath on exertion, bleeding and bone pain (4). AML develops rapidly and is fatal if not treated (5).

The incidence of AML in Europe is 5-8 cases per 100,000 people (4); in 2013, there were 2,942 new cases of AML in the UK (6). Incidence increases with age and median age of onset is 67 years (4). Between 2011 and 2013, about 55% of cases were diagnosed in people aged 70 years and over (6).

Guidelines on management of AML in adults have been published by the British Society for Haematology (7) and European LeukemiaNet (8).

- Newly diagnosed AML is treated in two phases – induction therapy with cytarabine and an anthracycline/anthracycline-like drug to induce remission, followed by consolidation with further chemotherapy or haematopoietic stem cell transplant (HSCT) to prevent relapse (7,8). In patients aged under 60 years, complete remission rates of 80% may be reached, with five-year overall survival about 40% (4). In older patients, remission rates are about 60%, but are usually transient with
median survival of five to 10 months and probability of remaining in remission five years after diagnosis being less than 10%. Patients failing to respond to one or two cycles of induction therapy are considered refractory and are at very high risk of ultimate treatment failure (4).

- Treatment of refractory or relapsed AML depends upon factors such as age, general health and cytogenetics, as well as duration of remission in cases of relapsed AML (5); those with an early relapse (duration of first remission less than six months), adverse (unfavourable) cytogenetics or older age have a poorer outcome (6). For people with good general health, treatment typically includes salvage chemotherapy and HSCT (5). The aim of salvage chemotherapy is to reduce the leukaemic burden or ‘bridge’ to HSCT. There is no generally accepted standard salvage therapy because of a lack of prospective controlled trials (8). People with relapsed AML may be offered the same chemotherapy to which the disease responded earlier, or other chemotherapy regimens containing intermediate-dose cytarabine (1g/m²) or high-dose cytarabine (2 to 3g/m²), as monotherapy or in combinations such as (5,7,8):
  - mitomycin, etoposide, and cytarabine (MEC) (5),
  - cladribine, cytarabine, mitoxantrone, and filgrastim (CLAG-M) (5),
  - fludarabine, cytarabine, idarubicin, and filgrastim (FLAG-Ida) (5),
  - daunorubicin or idarubicin and cytarabine (8), and
  - mitoxantrone and etoposide (8).

People with relapsed or refractory AML also receive supportive care which includes blood product replacement, antibiotics and antifungals (5). Patients who cannot have chemotherapy and HSCT are offered hydroxycarbamide (5,8) or low-dose cytarabine (7,8).

NICE is due to publish guidance on vosaroxin for refractory or relapsed AML in July 2017 (5). NICE has published guidance not recommending use of azacitidine for treating AML with more than 30% bone marrow blasts in people of 65 years or older who are not eligible for HSCT (9).

This evidence review considers recent evidence (published since 2012) for use of clofarabine in people with refractory or relapsed AML, and examines whether clofarabine allows them to undergo HSCT, thereby prolonging survival.
2. Summary of results

There is one randomised, controlled clinical trial of clofarabine in patients with refractory or relapsed AML (10). The CLASSIC I trial randomised 326 adults with relapsed or refractory AML to clofarabine 40mg/m² or placebo daily for five days, given as an intravenous infusion over one hour, followed three hours later by a two-hour infusion of cytarabine 1g/m².

Significantly more patients receiving clofarabine plus cytarabine achieved complete remission compared to patients receiving cytarabine monotherapy (35.2% vs. 17.8%; p<0.01). However, similar numbers of patients in each group subsequently underwent HSCT (about 20%). There was no significant difference between groups in the primary outcome of median overall survival (6.6 months with clofarabine plus cytarabine vs. 6.3 months with placebo plus cytarabine). Median disease-free survival was also similar between groups (8.1 months vs. 7.0 months, respectively). No comparison of post-transplant outcomes was reported for patients who did vs. those who did not go onto receive HSCT. The study enrolled patients aged at least 55 years, who had received no more than two previous induction regimens. It involved few European patients so the results may not be generalisable to the UK. In addition, the CLASSIC I trial was not designed to assess whether use of clofarabine allows more patients to undergo HSCT.

There was a high mortality rate of 16% in the first 30 days after administration of clofarabine and cytarabine, compared with 5% in patients treated with cytarabine alone (p<0.01). Deaths were mostly due to adverse events, and this might explain why an increase in complete remission rate did not translate into improved overall survival. Serious adverse events occurred in 60% of patients given clofarabine and cytarabine, and 49% given cytarabine alone. Serious infections occurred in 38% of patients given clofarabine and cytarabine compared with 22% of patients given cytarabine alone. Most common grade 3 to 4 adverse events in the clofarabine group were febrile neutropenia, hypokalaemia, thrombocytopenia, pneumonia, anaemia, neutropenia, and increased liver enzymes.

Uncontrolled studies using doses of clofarabine ranging from 15mg/m² to 40mg/m², alone or with cytarabine, show it can be used as a bridge for reducing leukaemic burden prior to HSCT in some patients. However, these findings are at high risk of bias and are limited by patient, disease and treatment heterogeneity.

The optimal role for clofarabine is unclear, and there are still questions to be answered about the balance between efficacy and toxicity of clofarabine. Insufficient evidence is available to determine the most appropriate dose and which patient groups are most likely to tolerate clofarabine.
3. Methodology

1. Scoping. A PICO was prepared by the Clinical and Public Health Leads for this policy area at NHS England (see section 10 below).
2. Appraisal. The following databases/sites were searched for relevant publications: The Cochrane Library, EMBASE, MEDLINE, NICE Evidence, National Guideline Clearinghouse (USA), UK National Library for Health guidelines database, the New Zealand Guidelines Group, the Australian National Health & Medical Research Council Guidelines Portal, UK National Institute of Health and Care Excellence (see sections 10 and 11 for search terms).
3. Titles and abstracts of results from literature searches were examined using criteria from the PICO. Full text versions of papers deemed to be useful or potentially useful were obtained and a decision made on the appropriateness of including their findings in this review.
4. Generally, where reasonable or good quality phase 3 studies were available, they were used in preference to earlier phase 1 and 2 studies. Three single-arm prospective studies and five retrospective studies considered relevant to the NHS in England were included. No cost-effectiveness analyses were identified.
5. Major, authoritative guidelines were examined and included where relevant.
6. The randomised controlled trial included in this evaluation was assessed for quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria, and for applicability of its results.
7. Evidence to support individual findings was graded.

4. Results

There is one randomised, controlled clinical trial of clofarabine in patients with refractory or relapsed AML (10).

- The CLASSIC I trial enrolled 326 adults aged at least 55 years (median 67 years; range 55 to 86), with refractory or relapsed AML after no more than two previous induction regimens (10). Patients were randomised to clofarabine 40mg/m² or placebo daily for five days, given as an intravenous infusion over one hour, followed three hours later by a two-hour infusion of cytarabine 1g/m² (a regimen known as CLARA). Patients who achieved remission after the induction cycle could receive a single (optional) consolidation cycle using the same regimen; patients who did not achieve remission but had haematological improvement could receive a second induction cycle followed by a consolidation cycle if required. Only 13 patients were from Europe and 44 from North America (no information provided on location of other patients). AML was centrally confirmed in 320 patients. Patients had to have adequate kidney and liver function and an Eastern Cooperative Oncology Group (ECOG)
performance status ≤2 (see Table 7 for baseline demographics). Patients were excluded if they had previously received clofarabine, or received HSCT or intermediate- or high-dose cytarabine in the previous three months. The primary outcome was overall survival, with follow-up continuing until 260 deaths occurred to achieve 90% power to detect a statistically significant difference between groups.

- Median overall survival was 6.6 months with clofarabine plus cytarabine and 6.3 months with placebo plus cytarabine (hazard ratio 1.0 [95% confidence interval, 0.78 to 1.28]; p=1.00). In patients with primary refractory AML or with a first pre-trial induction remission duration of less than six months (REF stratum, n=171), median overall survival was 5.1 months with clofarabine and 5.5 months with placebo (HR 1.13 [0.81 to 1.57]; p=0.47); in those with a pre-trial induction remission of six months or more (REL stratum, n=148), there was also no significant difference between groups (8.7 months vs. 7.2 months, respectively; 0.85 [0.58 to 1.24]; p=0.40).

- Clofarabine plus cytarabine was significantly more effective than placebo plus cytarabine for secondary outcomes of complete remission rate (35.2% vs. 17.8%; p<0.01), overall remission rate including complete and partial remission (46.9% vs. 22.9%; p<0.01), event-free survival (HR 0.63 [0.49 to 0.80]; p<0.01) and 4-month event-free survival rate (37.7% vs. 16.6%; p<0.01). However, median disease-free survival was similar in each group – 8.1 months vs. 7.0 months, respectively (no statistical analysis performed because of difference between groups in numbers of patients achieving remission).

- In an exploratory analysis, similar numbers of patients in each group subsequently underwent HSCT after study treatment (21% clofarabine vs. 19% placebo; p value not reported). At the time of transplant, 16% of patients treated with clofarabine were in remission and 9% of those in the placebo group. No post-transplant outcomes for the subgroup of patients undergoing HSCT were reported.

- All-cause 30-day induction mortality rate was 16% in the clofarabine group vs. 5% in the placebo group (p<0.01). Of the 25 patients in the clofarabine group who died within 30 days, five had disease progression, 19 died as a result of adverse events (AEs), and the cause of death of one patient was unknown. Among the 19 patients with fatal AEs, six died of sepsis-related AEs, three had respiratory distress/failure, two had a cerebral haemorrhage, two had pneumonia, and one patient each had a pulmonary haemorrhage, subdural haematoma, kidney failure, sinusoidal obstruction syndrome (previously known as veno-occlusive liver disease), acute myocardial infarction, and toxic epidermal necrolysis.

- Serious AEs were reported in 60% of patients receiving clofarabine compared with 49% in the placebo group, including serious infections (38% vs. 22%, respectively). In the clofarabine group, these serious infections included
bacteraemia (n=7), sepsis (n=8), pneumonia (n=13) and septic shock (n=6); in the placebo group they included cellulitis (n=3), bacteraemia (n=3) and pneumonia (n=12).

• There were similar rates of grade 3 to 4 AEs in the two groups (77% with clofarabine vs. 74% with placebo). Most common grade 3 to 4 AEs were febrile neutropenia, hypokalaemia, thrombocytopenia, pneumonia, anaemia, neutropenia, and increased aspartate transaminase (AST) and alanine transaminase (ALT). In the clofarabine group, incidences of grade 3 to 4 increased AST and ALT were 11% and 10% compared with 2% and 3%, respectively, with placebo.

• No quality of life data were collected.

In view of the lack of outcome data for patients undergoing HSCT after clofarabine induction therapy in the CLASSIC I trial, outcome data from relevant uncontrolled and retrospective studies are described narratively below. There are three single-arm prospective studies of clofarabine therapy used as a bridge to HSCT in adults with refractory or relapsed AML (11-13).

• Scappini et al. treated 47 adults (median age 50.5 years, range 21 to 71), who relapsed or failed to respond to at least two induction therapies including high-dose cytarabine, with clofarabine 22.5mg/m² followed after three hours by cytarabine 1g/m² daily for five days (11). Twenty-four patients (51%) achieved complete remission (14 after one course and 10 after a further consolidation course). Thirteen patients (28%) underwent allogeneic bone marrow transplantation. Transplant was not an option for 11 patients because of lack of donor, older age or early relapse. Median overall survival in transplanted patients was 445 days (range 30 to 1,531 days) – equivalent to 14.8 months. This compares with a median overall survival in all 47 patients of 197 days (range 4 to 1,531 days) – equivalent to 6.6 months. Six patients died during induction (13%). Most common AEs were nausea, vomiting, diarrhoea, skin rash, transient increases in transaminases and bilirubin, febrile neutropenia and infections. Two patients had reactivation of herpes infection, prompting the investigators to introduce use of aciclovir prophylaxis during the study.

• Locke et al. gave clofarabine 30mg/m² daily for five days to 29 adults (median age 51 years, range 23 to 69) with refractory or relapsed AML (n=16), myelodysplastic syndrome (MDS, n=8), myeloproliferative disorder (n=3) or acute lymphoblastic leukaemia (n=2) (12). A cytoreductive response (bone marrow biopsy with cellularity less than 20% and blasts less than 10%) was achieved in 52% of patients (54% of the AML/MDS subset). Conditioning regimens for allogeneic HSCT began in 26 patients at their haematological nadir (12 to 21 days after starting clofarabine); in two patients HSCT was delayed because of infection and progressive disease, and both later received high-dose cytarabine plus mitoxantrone prior to HSCT. In the 23 AML/MDS
patients (96%) who subsequently underwent HSCT, median overall survival was 373 days (95% CI >220) – equivalent to 12.4 months. Median progression-free survival was 251 days (173 to 358) – equivalent to 8.4 months. Six-month and one-year overall survival rates were 78% (55 to 90) and 52% (31 to 70), and progression-free survival at one year was 26% (11 to 45). Non-relapse mortality at 100 days was 0%. Grade 3 or 4 AEs reported after clofarabine but before conditioning included increased transaminases (24%), infections (10%) and transient hyperbilirubinaemia (7%).

- In the BRIDGE trial, Middeke et al. treated 84 patients with refractory AML (49%) or in first relapse (median age 61 years, range 40 to 75) with at least one cycle of clofarabine 30mg/m² plus cytarabine 1g/m² daily for five days – the dose of clofarabine was reduced from 40mg/m² after 25 patients were treated, based on preliminary results of the CLASSIC I trial (13). Nineteen patients (23%) had ECOG performance status ≥2. Sixty-six patients (79%) with at least a moderate response at day 15 (marked reduction in percentage of leukaemic blasts in bone marrow or in bone marrow cellularity and absence of blasts in peripheral blood) received a conditioning regimen of clofarabine 30mg/m² daily for four days and a single dose of melphalan IV 140mg/m². 57 patients (68%) with a suitable donor underwent HSCT. Overall, 50 patients (60%) achieved treatment success, defined as complete remission (n=29, 35%), partial remission (n=11, 13%) or complete remission by chimerism (n=10, 12%). Two-year overall survival rate for all enrolled patients was 43% (95% CI 33 to 55); rates were 35% in those with refractory AML and 50% in those with relapsed AML. Disease-free survival rate in the 50 patients who achieved treatment success was 52% (39 to 68) at two years. Non-relapse mortality at two years was 23% (11 to 35). Grade 3 or 4 AEs reported after the first course of CLARA included transient increases in transaminases or bilirubin in 53% of patients, infection in 45% and hand-foot syndrome in 10%. All-cause early death rate at 30 days was 10% due to septic multi-organ failure or persistent disease.

There are five retrospective US or German studies of clofarabine therapy used as a bridge to HSCT in adults with refractory of relapsed AML (14-18).

- Buchholz et al. reported a two-year overall survival rate of 56% in 27 adults with high-risk AML (n=20) or advanced MDS (median age 58 years, range 19 to 69), who underwent allogeneic HSCT after treatment with clofarabine 30mg/m² and cytarabine 1g/m² daily for five days, followed five days later by reduced-intensity conditioning (14). Five patients (19%) achieved complete remission prior to HSCT. Twenty-two patients (81%) were alive 30 days after HSCT, and all of these achieved either complete or partial remission by day 50. Relapse-free survival rate was 52% at two years. All patients developed grade 4 haematological toxicity, and 17 patients (63%) had grade 3 or 4 increases in AST or ALT, which were transient in every patient except one who developed sinusoidal obstruction syndrome and later died from multi-organ failure. Grade 3 hand-foot syndrome occurred in two patients and 13 patients had infection,
including one case of aciclovir-resistant herpes simplex infection of the eyes. Non-relapse mortality was 35% at two years.

• Tischer et al. treated 15 adults with AML and three with acute lymphoblastic leukaemia (median age 39 years, range 20 to 69) with clofarabine 30mg/m² daily for five days, three days prior to conditioning and then haploidentical HSCT (from a partially HLA-matched family donor) (15). Complete remission was achieved by 78% of patients one month after transplant. After a median follow-up of 19 months, overall survival and relapse-free survival at one year were 56% (95% CI 31 to 74) and 39% (18 to 60), respectively. No patients died during induction therapy or conditioning. Non-relapse mortality at one year was 23% and infection was contributory in all cases – the authors considered this high rate could be due to the high number of intensively pre-treated patients. Grade 3 or 4 AEs included transient increases in liver enzymes (44%), mucositis (40%), hand-foot syndrome (17%), increased creatinine (17%) and nausea/vomiting (17%).

• Loeffler et al. compared outcomes of 59 successive patients (median age 57 years, range 21 to 75) who received clofarabine 40mg/m² on days 2 to 6 plus cytarabine 1g/m² on days 1 to 5 (n=32) or S-HAM (cytarabine 2 x 1g/m² on days 1, 2, 8 and 9, plus mitoxantrone 10mg/m² on days 3, 4, 10 and 11, n=18) or MTC (mitoxantrone 12mg/m² on days 1 and 2, plus cytarabine 1g/m² on days 3 to 7, plus topotecan 1.5mg/m² on days 3 to 7, n=9) (16). Assignment was not randomised but based on date of diagnosis. Blast clearance was achieved in 69% in the clofarabine group, 61.1% in the S-HAM group and 12.5% in the MTC group; however, blast clearance was not a positive predictor for survival. 18 patients (31%) died prior to HSCT, 17 due to infection complications (29%), and one patient died due to refractory disease. Forty patients (67.8%) underwent allogeneic HSCT (starting conditioning at their haematological nadir) including 22 who received clofarabine, 14 who received S-HAM and four who received MTC. Survival during a median follow-up of 135 days was 22.2% (n=7/32; one unknown) in the clofarabine group, 43.7% (n=7/18; two unknown) in the S-HAM group, and 22.2% (n=2/9) in the MTC group. Of note, 41% of patients in the clofarabine group, 28% in the S-HAM group and 75% in the MTC group, did not receive a HLA-identical graft. This is associated with a potentially higher transplant-related mortality rate. AEs reported in patients receiving clofarabine were gastrointestinal symptoms, hand-foot syndrome, transient increases in liver enzymes and infections (rates not reported).

• Thomas et al. reported a one-year overall survival rate of 32% (95% CI 14 to 50), with a median follow-up of 35 months (32 to 45) in 22 adults with AML and three with MDS (median age 60 years, range 21 to 71) who received clofarabine 30mg/m² daily for five days (17). Twenty-one (84%) received HSCT during aplasia within 15 to 21 days of completing clofarabine; one-year overall survival rate in these patients was 42% (20 to 64) with a median overall survival of 233 days (equivalent to 7.8 months). Progression-free survival at one year was 33% (13 to 53). Four patients did not receive a transplant
because of sepsis (n=3) and death due to multi-organ failure. Incidence of non-relapse mortality was 19% at one year (2 to 37). Nineteen patients (76%) experienced grade 3 or 4 AEs, including increased AST (28%) and ALT (24%) levels between bridge and transplant.

• Roberts et al. reviewed outcomes in 81 adults with AML and three with MDS (median age 51 years, range 22 to 77) who received either clofarabine (30 or 40mg/m²) plus cytarabine 1g/m² daily for five days (n=65), or clofarabine monotherapy (doses ranging from 15 to 30mg/m² daily for five days, n=19) (18). Thirteen patients (15%) had ECOG performance status ≥2. Complete remission rate was 14% (95% CI 8.2 to 24) and overall median survival was three months (no CIs reported); a subset of 12 patients who received allogeneic HSCT had a median overall survival of 18 months. Nine of these patients were in complete remission at the time of transplant. Mortality rate within 30 days of receiving clofarabine was 21%. 82% of patients had raised liver function tests (88% clofarabine plus cytarabine vs. 63% clofarabine monotherapy) and 70% experienced infection (75% vs. 53%, respectively). Of 54 infections where a specific organism was documented, 19 were fungal or viral. The authors conducted a meta-analysis of previous PI and PII studies assessing clofarabine in patients with refractory or relapsed AML or MDS, plus the CLASSIC I trial, to explore differences between their real-world analysis and trial findings, with the caveat that these trials had differing eligibility criteria and other protocol characteristics – they calculated a complete remission rate of 35% (95% CI 30 to 39). Detailed methods of how relevant studies were identified and how the meta-analysis was conducted were not stated, and no information was provided on clofarabine regimens used and numbers of patients undergoing HSCT.

5. Discussion

The research question posed by the Policy Working Group was:
• Does clofarabine improve response rate in patients with refractory or relapsed AML allowing them to undergo stem cell transplantation and thereby prolong survival?

Evidence for efficacy of clofarabine
One published double-blind, randomised placebo-controlled trial (CLASSIC I) assessed the efficacy and safety of clofarabine added to cytarabine as induction therapy for 326 adults with refractory or relapsed AML (10). Significantly more patients receiving clofarabine and cytarabine achieved complete remission compared with patients receiving cytarabine monotherapy (35.2% vs. 17.8%; p<0.01). However, similar numbers of patients in each group subsequently underwent HSCT (about 20%), and there was no significant difference between
groups in median overall survival (6.6 months with clofarabine plus cytarabine vs. 6.3 months with placebo plus cytarabine). Median disease-free survival was also similar between groups (8.1 months vs. 7.0 months, respectively). Reporting of outcomes in patients who subsequently underwent HSCT after induction therapy was limited to the numbers who received a transplant and the proportion in remission at the time of transplant; no statistical analysis of post-transplant outcomes in this patient group was reported. There was also no information on source and timing of transplants, donor types and conditioning regimens used.

The population in CLASSIC I was highly selected. It included patients aged at least 55 years (median age 67) with relatively good performance status (ECOG ≤2) and adequate kidney and liver function, who had previously received no more than two induction regimens, and had not received intermediate- or high-dose cytarabine, or HSCT in the previous three months. The authors of one retrospective study (18) noted that only ten of the 65 patients who received clofarabine and cytarabine in their study would have been eligible for CLASSIC I, mostly because of younger age. In CLASSIC I, there were slightly more patients in the clofarabine group than in the placebo group with unfavourable/other cytogenetics (49.4% vs. 38.6%, respectively) and worse performance status (ECOG 2, 16.0% vs. 11.4%, respectively), indicating they were possibly less likely to respond to or tolerate treatment, but otherwise baseline characteristics were similar between groups (10). Nearly half the patients in each group had primary refractory AML. BSH guidelines note that in older patients aged over 60-65 years with adverse cytogenetics who relapse within six months of chemotherapy, the likelihood of durable response to salvage treatment is extremely low (7). Only 13 patients were recruited in Europe so the study findings may not be generalisable to the UK. No information was provided on intensity of previous induction therapy, including previous HSCT, which is an important factor in deciding on subsequent care (19). Neither was there information on co-morbidities. Co-morbidities, such as diabetes, coronary heart disease and chronic obstructive pulmonary disease (20), are predictive of early death rates and reduced overall survival in people with AML (8).

Clofarabine has been proposed as a therapy that could enable more refractory or relapsed patients to achieve good disease control prior to HSCT (21). There is preliminary evidence from uncontrolled studies that use of clofarabine, with or without intermediate-dose cytarabine, allows some patients to proceed to HSCT, but it does not show that clofarabine increases the numbers of patients undergoing transplant or that it is responsible for prolonged survival (11-15,17-18). All of these studies have small sample sizes, are at high risk of bias, and are limited by patient and disease heterogeneity, and variability in transplant characteristics, conditioning regimens, donor sources and graft versus host disease prophylaxis, in addition to usual selection or reporting biases for open-label, non-randomised studies. The studies included patients aged 19 to 75 years, who had failed to respond to up to four previous induction regimens. Performance status was rarely reported, but two studies include patients with ECOG status ≥2 (13,18). They used a variety of clofarabine doses, ranging from 15mg/m² to 40mg/m². A single-arm prospective study involving 47 heavily-pre-treated patients given clofarabine and cytarabine
showed median overall survival was 14.8 months in a subgroup of 13 patients who achieved complete remission and underwent HSCT, compared with 6.6 months in the study population overall (11). A retrospective analysis reported median overall survival of three months in 81 patients given clofarabine (as monotherapy or combination therapy with cytarabine), compared with 18 months in 12 patients who subsequently received a transplant, nine of whom were in complete remission at the time of transplant (18). No statistical analysis of these data is available from either study. In other uncontrolled studies, overall survival rates in patients undergoing HSCT after clofarabine salvage therapy ranged from 32% to 56% at one year (15,17), and 43% to 56% at two years (13,14). Complete remission rates were also variable, from 35% to 78% (13,15). CLASSIC I did not report overall survival rates for the subgroup of patients who proceeded to HSCT (10); for all enrolled patients, overall survival at two years was estimated by other investigators to be about 10% (13), a rate much lower than reported in uncontrolled studies. A retrospective study involving 59 patients showed that clofarabine was not associated with improved survival compared to two mitoxantrone-containing regimens (16). Of note, guidelines recommend that the aim of induction therapy in refractory or relapsed AML is to achieve a new remission before undergoing HSCT (7,8,20,22). However, it is unclear how important complete remission prior to HSCT is – in only one of the uncontrolled or retrospective studies did all patients achieve complete remission before start of conditioning (11); in five studies conditioning regimens began as soon as patients were at their haematological nadir or in aplasia (12-14,16-17), and in another study conditioning started three days after finishing clofarabine (15) – this was done in an attempt to minimise toxicity from repeated cycles of chemotherapy needed to achieve remission.

Clofarabine is not included in British or European AML guidelines (7,8,20). For patients with refractory or relapsed AML, European LeukemiaNet guidelines recommend cytarabine (if not used for first induction), with or without an anthracycline (8). Mitoxantrone plus etoposide and cytarabine (MEC) is another option for relapsed disease.

More recently published US guidelines recommend several regimens for refractory or relapsed patients able to tolerate aggressive therapy, and clofarabine (alone, or in doses of 22.5mg/m² to 25mg/m² daily for five days in combination with other agents) is included (22). Supporting evidence is from two uncontrolled studies – a phase I study published in 2008 (23) and a phase I/II study published in 2011 (24). The CLASSIC I study is discussed within US guidelines and the dosing regimen used classed as an aggressive regimen, however it is not listed as a recommended regimen.
Evidence for safety of clofarabine

In CLASSIC I, there was a significantly higher early mortality rate of 16% in patients treated with clofarabine and cytarabine compared with 5% with placebo plus cytarabine. The authors suggested that this might be because the regimen was too toxic for some patients, and might explain why an increase in complete remission rates did not translate into improved overall survival. In addition, the clofarabine dose may have been too high. However, the study did not report findings for subgroups grouped by risk factors for treatment-related mortality (such as older age and co-morbidities), and so did not identify which patient groups are most at risk of toxicity. It is known that older patients are more likely than younger patients to suffer treatment-related early death (8). In the single-arm and retrospective studies described above, induction-related or all-cause 30-day mortality was 0% with clofarabine monotherapy (12,15), 13% with combination therapy using clofarabine doses of 22.5mg/m² (11), and 10% to 31% with clofarabine 30 to 40mg/m² plus cytarabine (13,16). Most studies reported treatment-related mortality at one or two years (12-17) but it is not possible to separate adverse events associated with the transplant from those due to induction therapy.

Clofarabine causes significant immunosuppression and was associated with viral and fungal infections in several studies, necessitating use of prophylaxis. In a retrospective ‘real-world’ review of clofarabine monotherapy and combination therapy with cytarabine, in which use of antibiotic prophylaxis varied widely, the incidence of febrile neutropenia and infections in the combination therapy group were 90% and 75%, respectively (18). The authors noted 19 fungal or viral infections, and highlighted another study suggesting rates of non-bacterial infections are higher with clofarabine than with fludarabine or other salvage regimens. In CLASSIC I, use of prophylactic antibiotics, antifungals and antivirals was recommended. 60% of patients receiving clofarabine had a serious AE compared with 49% in the placebo group, including serious infections (38% vs. 22%, respectively) (10). In the clofarabine group, these infections included bacteraemia, sepsis, pneumonia and septic shock. No cases of fungal or viral infection were reported.

Clofarabine can also cause significant hepatotoxicity, and there are concerns about the possibility of post-transplant hepatotoxicity (18). In CLASSIC I, patients receiving clofarabine plus cytarabine had higher rates of grade 3 to 4 increased ALT or AST (10% and 11%, respectively) compared with patients receiving placebo and cytarabine (3% and 2%, respectively). There was one death due to hepatotoxicity (sinusoidal obstruction syndrome). Increases in transaminases and/or bilirubin were reported to be common in most of the single-arm and retrospective studies described above (11-15,17,18), with rates of grade 3 or 4 increases ranging from 24% to 53% (12,13). The higher rates in these studies, compared to the rate in CLASSIC I, may be due to the inclusion of more patients with comorbidities. However, there was no evidence of sustained liver damage or higher than expected rates of sinusoidal obstruction syndrome in these studies.
6. Conclusion

The optimal role for clofarabine is unclear.

There is only one randomised controlled trial of clofarabine in refractory or relapsed AML in older adults aged at least 55 years, and this showed that adding clofarabine 40mg/m² daily for five days to treatment with cytarabine does not allow more patients to undergo HSCT or improve overall survival. However, the study was not designed to assess whether use of clofarabine allows more patients to undergo HSCT. More patients achieved complete remission with clofarabine and cytarabine than with cytarabine alone, but this was offset by more deaths due to adverse events. No comparison of post-transplant outcomes was reported for patients who did vs. those who did not go onto to receive HSCT.

Uncontrolled studies using doses of clofarabine ranging from 15mg/m² to 40mg/m², alone or with cytarabine, show it can be used as a bridge for reducing leukaemic burden prior to HSCT in some patients. However, these findings are at high risk of bias and are limited by patient, disease and treatment heterogeneity.

There are still questions to be answered about the balance between efficacy and toxicity of clofarabine. Further studies are needed to establish the most appropriate dose and which patient groups are most likely to tolerate clofarabine.
## 7. Evidence Summary Table

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Study Design</th>
<th>Population characteristics</th>
<th>Intervention</th>
<th>Outcome measure type</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Quality of Evidence Score</th>
<th>Applicability</th>
<th>Critical Appraisal Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faderl et al 2012</td>
<td>Double-blind, multi-centre (57), randomised (1:1), controlled, phase 3 trial</td>
<td>326 adults aged ≥55 years (median 67; range 55 to 86) with refractory or relapsed, blinded and centrally-confirmed AML (≥5% blasts) after ≤2 previous induction regimens, and ECOG performance status 0-2.</td>
<td>Arm 1 (n=162): Clofarabine 40mg/m² IV infusion over 1 hour followed 3 hours later by cytarabine 1g/m² IV infusion over 2 hours, daily for 5 consecutive days.</td>
<td>Primary Clinical effectiveness</td>
<td>Overall survival (OS), median – defined as time from randomisation to date of death from any cause, or date last known to be alive. 90% power achieved once 260 deaths occurred.</td>
<td>Clofarabine 6.6 months vs. placebo 6.3 months (HR 1.00 [95% CI 0.78 to 1.28]; p=1.0); median follow-up 6.9 vs. 6.4 months, respectively.</td>
<td>8</td>
<td>Direct study that focuses on the indication of interest.</td>
<td>A double-blind, randomised study involving a subset of the population of interest. Patients aged at least 55 years with adequate kidney and liver function were enrolled, with a maximum of two previous failed induction regimens. Previous use of intermediate- or high-dose cytarabine was not exceeded three months. Previous HSCT within the previous 3 months was also not permitted. About 90% of patients were white but only 13 were recruited in Europe, so this could affect how generalisable the results are to patients in the UK. Patient demographics were balanced between groups, except more patients receiving clofarabine than receiving placebo had unfavourable cytogenetics (49.4% vs. 38.6%, respectively) and ECOG PS 2 (16% vs. 11.4%, respectively). No information was available on medical co-morbidities.</td>
</tr>
<tr>
<td></td>
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<td>Follow-up</td>
<td>5 clofarabine patients and 1 placebo patient excluded from efficacy and safety analysis because AML diagnosis not centrally confirmed.</td>
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<td>1 clofarabine patient and 3 placebo patients excluded from</td>
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<td>Arm 2 (n=158): Placebo IV infusion over 1 hour followed 3 hours later by cytarabine 1g/m² IV infusion over 2 hours, daily for 5 consecutive days.</td>
<td>Secondary Clinical effectiveness</td>
<td>Complete remission (CR), % – defined as recovery to normal haematopoiesis, absolute neutrophil count ≥1.0 x 10⁹/L, platelet count ≥100 x 10⁹/L and normalisation of marrow blasts (&lt;5%).</td>
<td>Clofarabine 35.2% vs. placebo 17.8% (p&lt;0.01)</td>
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<td>39 patients who achieved remission after</td>
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<td>the first cycle received a second cycle as consolidation therapy (24.2%)</td>
<td>Secondary Clinical effectiveness</td>
<td>Complete response with incomplete peripheral blood count recovery (CRi), % – defined as recovery to normal haematopoiesis and normalisation of marrow blasts (&lt;5%).</td>
<td>Clofarabine 11.7% vs. placebo 5.0% (p value not reported)</td>
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<td>35 patients who achieved remission after the first cycle received a second cycle as consolidation therapy (24.2%)</td>
<td></td>
<td>Secondary Clinical effectiveness</td>
<td>Complete response with incomplete peripheral blood count recovery (CRi), % – defined as recovery to normal haematopoiesis and normalisation of marrow blasts (&lt;5%).</td>
<td>Clofarabine 12.5% vs. placebo 4.8% (p value not reported)</td>
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<td></td>
<td></td>
<td>35 patients who achieved remission after the first cycle received a second cycle as consolidation therapy (24.2%)</td>
<td></td>
<td>Secondary Clinical effectiveness</td>
<td>Complete response with incomplete peripheral blood count recovery (CRi), % – defined as recovery to normal haematopoiesis and normalisation of marrow blasts (&lt;5%).</td>
<td>Clofarabine 10.8% vs. placebo 5.4% (p value not reported)</td>
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</tbody>
</table>

Clofarabine in refractory or relapsed AML UKMi final
Use of clofarabine plus cytarabine versus placebo plus cytarabine to treat refractory or relapsed AML (CLASSIC I)

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Study Design</th>
<th>Population characteristics</th>
<th>Intervention</th>
<th>Outcome measure type</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Quality of Evidence Score</th>
<th>Applicability</th>
<th>Critical Appraisal Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety analysis because they did not receive study treatment.</td>
<td>clofarabine vs. 16.1% placebo.</td>
<td>94 patients who did not achieve remission after the first cycle but had haematological improvement received a second cycle as re-induction (6.8% clofarabine vs. 12.3% placebo) and a third cycle as consolidation (1.9% vs. 2.6%, respectively).</td>
<td>Secondary Clinical effectiveness</td>
<td>Overall remission rate (ORR), % – defined as CR + CRi.</td>
<td>Clofarabine 46.9% vs. placebo 22.9% (p&lt;0.01)</td>
<td>REF stratum Clofarabine 45.5% vs. placebo 22.9% (p&lt;0.01) REL stratum Clofarabine 48.6% vs. placebo 23.0% (p&lt;0.01)</td>
<td>Allocation to treatment groups was concealed by central randomisation using an interactive voice-response system, minimising risk of bias. Follow-up in the study was endpoint-driven (until 260 deaths occurred) and was designed to achieve 90% power to detect a statistically significant difference in overall survival – this was almost achieved, with 258 deaths documented. Loss to follow-up was minimal (1 clofarabine vs. 3 placebo). Choice of comparator is appropriate; British Society for Haematology guidelines note that the mainstay of therapy for refractory or relapsed disease is low- (100 to 200mg/m²), intermediate- (1g/m²) or high-dose cytarabine (2 to 3g/m²), and in combination with other drugs including fludarabine (7). Treatment response was assessed according to International Working group.</td>
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<tr>
<td>Baseline data</td>
<td>Clofarabine White 92.6% ECOG 216% Unfavourable/other cytogenetics 49.4%</td>
<td>Placebo White 89.9% ECOG 211.4% Unfavourable/other cytogenetics 38.6%</td>
<td>Stratified into two groups: REF (n=171) primary refractory disease or first</td>
<td>Secondary Clinical effectiveness</td>
<td>Total duration of remission (DOR), median – defined as time from documented remission to time of death, relapse or initiation of alternative antileukaemic therapy while in remission.</td>
<td>Clofarabine 7.6 months vs. placebo 3.8 months REF stratum Clofarabine 5.7 months vs. placebo 6.3 months REL stratum Clofarabine 11.5 months vs. placebo 3.8 months</td>
<td>No statistical analysis performed because of difference in numbers of patients in each group achieving remission.</td>
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<td>Secondary Clinical effectiveness</td>
<td>Disease-free survival (DFS), median – defined as time from IRRP-documented remission to time of death or relapse.</td>
<td>Clofarabine 8.1 months vs. placebo 7.0 months REF stratum Clofarabine 5.7 months vs. placebo 6.7 months REL stratum Clofarabine 10.3 months vs. placebo 9.1 months</td>
<td>No statistical analysis performed because of difference in numbers of patients in each group achieving remission.</td>
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</tbody>
</table>

Clofarabine in refractory or relapsed AML UKMi final
**Use of clofarabine plus cytarabine versus placebo plus cytarabine to treat refractory or relapsed AML (CLASSIC I)**

See bottom of table for key of abbreviations

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Study Design</th>
<th>Population characteristics</th>
<th>Intervention</th>
<th>Outcome measure type</th>
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<th>Results</th>
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<th>Applicability</th>
<th>Critical Appraisal Summary</th>
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<tbody>
<tr>
<td></td>
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<td>Pre-trial induction remission (CR1) &lt;6 months, • REL (n=148) relapse duration after CR1 ≥6 months.</td>
<td>Secondary Clinical effectiveness</td>
<td>Event-free survival (EFS), % – defined as months from randomisation to time of treatment failure, relapse, death or date last known to be alive and in remission.</td>
<td>Clofarabine 80.2% vs. placebo 91.7% (HR 0.63 [0.49 to 0.80]; p&lt;0.01) REF stratum Clofarabine 83.0% vs. placebo 94.0% (HR 0.67 [0.49 to 0.93]; p=0.013) REF stratum Clofarabine 77.0% vs. placebo 89.2% (HR 0.57 [0.40 to 0.83]; p&lt;0.01)</td>
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<td>criteria, by an Independent-response review panel. Patients who did not achieve CR or CRi during induction or re-induction were considered treatment failures. An independent data monitoring committee assessed serious AEs every three months and full safety results (all AEs and laboratory findings) every six months. 64 patients subsequently underwent HSCT. Reasons for not progressing to HSCT were not stated. No information was provided on the conditioning regimens used prior to HSCT and when it was performed in relation to the completion of the induction and/or consolidation cycle. All but two patients received an allogeneic HSCT. No comparison of post-transplant outcomes was reported for patients who did vs. those who did not go onto to receive HSCT.</td>
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<td>Secondary Clinical effectiveness</td>
<td>4-month event-free survival (EFS), %</td>
<td>Clofarabine 37.7% vs. placebo 16.6% (p&lt;0.01) REF stratum Clofarabine 35.2% vs. placebo 16.9% (p&lt;0.01) REF stratum Clofarabine 40.5% vs. placebo 16.2% (p&lt;0.01)</td>
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<td></td>
<td></td>
<td></td>
<td>Secondary Safety</td>
<td>Adverse events (AEs)</td>
<td>All-cause 30-day mortality Clofarabine 16% vs. placebo 5% Serious AEs Clofarabine 60% vs. placebo 49% including serious infections 38% vs. 22% Grade 3 to 4 toxicities (Clofarabine vs. placebo) • febrile neutropenia 47% vs. 35% • hypokalaemia 18% vs. 11% • thrombocytopenia 16% vs. 17% • pneumonia 14% vs. 10% • anaemia 13% vs. 8% • neutropenia 11% vs. 9% • raised AST 11% vs. 2% • raised ALT 10% vs. 3%</td>
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</table>
### Use of clofarabine plus cytarabine versus placebo plus cytarabine to treat refractory or relapsed AML (CLASSIC I)

See bottom of table for key of abbreviations.

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Study Design</th>
<th>Population characteristics</th>
<th>Intervention</th>
<th>Outcome measure type</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Quality of Evidence Score</th>
<th>Applicability</th>
<th>Critical Appraisal Summary</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td>Exploratory Clinical effectiveness</td>
<td>HSCT after study treatment, %</td>
<td>Clofarabine 21% vs. placebo 19% (p value not reported)</td>
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<td></td>
<td>Remission at the time of HSCT, %</td>
<td>Clofarabine 16% vs. placebo 9% (p value not reported)</td>
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</tbody>
</table>

**KEY.** AE: adverse event; AST: aspartate transaminase; ALT: alanine transaminase; CR: complete remission; CRi: complete remission with incomplete peripheral blood count recovery; DFS: disease-free survival; DOR: duration of remission; ECOG: Eastern Cooperative Oncology Group; EFS: event-free survival; HSCT: haematopoietic stem cell transplant; IRRP: independent-response review panel; ORR: overall remission rate; OS: overall survival; REF: primary refractory disease or first pre-trial induction remission (CR1) <6 months; REL: relapse duration after CR1 ≥6 months.
## 8. Grade of evidence table

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Reference</th>
<th>Quality of Evidence Score</th>
<th>Applicability</th>
<th>Grade of Evidence</th>
<th>Interpretation of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival (OS), median</td>
<td>Faderl et al 2012</td>
<td>8</td>
<td>Direct study</td>
<td>B</td>
<td>In the only randomised trial comparing clofarabine with another salvage chemotherapy in adults aged 55 years or older with refractory or relapsed AML, patients given clofarabine and cytarabine had a median OS of 6.6 months compared with 6.3 months in patients given placebo plus cytarabine. The difference of 0.3 months between the groups was not statistically significant. OS was the primary outcome in this study, and was defined as time from randomisation to date of death from any cause, or date last known to be alive. The study had almost 90% power to detect a statistically significant difference between groups, with 258 deaths of the 260 required documented, and outcomes were confirmed by an independent response review panel.</td>
</tr>
<tr>
<td>Complete remission (CR), %</td>
<td>Faderl et al 2012</td>
<td>8</td>
<td>Direct study</td>
<td>B</td>
<td>In the only randomised trial, significantly more patients treated with clofarabine plus cytarabine went into CR than patients treated with cytarabine alone – rates were 35.2% and 17.8%, respectively. CR was defined as recovery to normal haematopoiesis, absolute neutrophil count ≥1.0 x 10^9/L, platelet count ≥100 x 10^9/L, and normalisation of marrow blasts (&lt;5%). CR in each patient was confirmed by an independent response review panel.</td>
</tr>
<tr>
<td>Disease-free survival (DFS), median</td>
<td>Faderl et al 2012</td>
<td>8</td>
<td>Direct study</td>
<td>B</td>
<td>In the only randomised trial, treatment with clofarabine plus cytarabine did not increase the time patients were free of disease compared with treatment with cytarabine alone. Median DFS was 8.1 months in the group given clofarabine and cytarabine, and was 7.0 months in the group given placebo plus cytarabine. DFS was defined according to international criteria, and was confirmed in each patient by an independent response review panel. No statistical analysis of this outcome was done because of difference in numbers of patients in each group achieving remission.</td>
</tr>
<tr>
<td>All-cause 30-day mortality, %</td>
<td>Faderl et al 2012</td>
<td>8</td>
<td>Direct study</td>
<td>B</td>
<td>In the only randomised trial, 25 patients (16%) died from any cause within 30 days of receiving clofarabine and cytarabine, and eight (5%) died in the group given placebo and cytarabine. This was a statistically significant difference between groups. Most patients given clofarabine died because of adverse events (AEs) – 19 died of AEs, five had disease progression and cause of death was unknown in one patient. Reason for death was not stated for patients in the comparator group.</td>
</tr>
<tr>
<td>Adverse events (AEs), %</td>
<td>Faderl et al 2012</td>
<td>8</td>
<td>Direct study</td>
<td>B</td>
<td>In the only randomised trial, 60% of patients receiving clofarabine and cytarabine had a serious AE compared with 49% given cytarabine. This included a higher rate of serious infections with clofarabine and cytarabine (38%) than with cytarabine alone (22%). There were similar rates of grade 3 to 4 AEs in the two groups (77% with clofarabine and cytarabine vs. 74% with cytarabine alone). However, more patients in the clofarabine group had increased liver enzymes. The rates of increased AST and ALT were 11% and 10% with clofarabine and cytarabine, compared with 2% and 3%, respectively, with cytarabine alone.</td>
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</tbody>
</table>

Clofarabine in refractory or relapsed AML UKmi final
## 9. Fact Sheet

**Intervention Fact Sheet**

<table>
<thead>
<tr>
<th>What is the intervention for?</th>
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<tbody>
<tr>
<td>Who might consider taking it?</td>
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<tr>
<td>Who should not take it?</td>
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<tr>
<td>Other things to consider</td>
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<tr>
<td>Benefits</td>
<td>Placebo/comparator</td>
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<tr>
<td>What difference did the intervention make?</td>
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<tr>
<td>Include questions based on outcomes measures report</td>
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<tr>
<td>• For. e.g. What was the change in pulmonary vascular resistance?</td>
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<td>Harms</td>
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<tr>
<td>Did the intervention have side effects?</td>
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<tr>
<td>Include questions based on outcomes measures report</td>
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<tr>
<td>• For. e.g. Were there life-threatening side effects?</td>
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</table>
10. Literature Search Terms

<table>
<thead>
<tr>
<th><strong>Search strategy</strong></th>
<th>Indicate all terms to be used in the search</th>
</tr>
</thead>
</table>
| **P – Patients / Population** | Clofarabine, evoltra, clolar, acute myeloid leukaemia, acute myelogenous leukaemia, acute non lymphocytic leukaemia, acute granulocytic, relapsed, refractory, treatment*, therap*, medication, medicines, drug*, clofarabine and acute myeloid leukaemia  
Patients aged 18 years and above who have not responded to first line treatment or who have relapsed post first line treatment |
| **I – Intervention** | Clofarabine (Evoltra; Clolar) belongs to a group of drugs known as anti-metabolites that interfere with the growth of cancer cells and cause them to die. Clofarabine is administered as an intravenous infusion usually in combination with other chemotherapy agents. |
| **C – Comparison** | The main alternatives are:  
• First line therapies: no current standard of care at this point in disease process  
• High Dose Cytarabine ,Novel agent via clinical trial or Best Supportive Care |
| **O – Outcomes** | Critical to decision-making:  
• Complete Remission (CR) rate  
• Progression free survival (PFS)  
• Overall Survival (OS)  
Important to decision-making:  
• Safety measures e.g. adverse events, abnormal laboratory indices.  
• Evidence of treatment failure e.g. XXXXX  
• Measures of cost-effectiveness e.g. incremental cost effectiveness ratio (ICER).  
• Measures of unplanned health care e.g. emergency admissions |

Clofarabine in refractory or relapsed AML UKMi final
### Assumptions / limits applied to search

| Inclusion Criteria                                                                 | Articles published in English in peer reviewed journals in the last 5 years (2012 onwards) that include ADULT patients (aged 18 years and above) with refractory or relapsed AML  
Study types:  
• Systematic review and meta-analysis  
• RCT |
|---|---|
| Exclusion Criteria                                                                 | Not English language  
Animal studies  
Non-peer reviewed literature  
>5 years (pre-2012) |

### 11. Search Strategy

**Embase**

1. EMBASE; CLOFARABINE/; 1805 results.
2. EMBASE; evoltra.af; 65 results.
3. EMBASE; clolar.af; 105 results.
4. EMBASE; 1 OR 2 OR 3; 1806 results.
5. EMBASE; ACUTE MYELOBLASTIC LEUKEMIA/; 11750 results.
6. EMBASE; relapsed.af; 48338 results.
7. EMBASE; refractory.af; 148071 results.
8. EMBASE; 6 OR 7; 180711 results.
9. EMBASE; 4 AND 5 AND 8; 42 results.
10. EMBASE; treatment*.af; 5400788 results.
11. EMBASE; therap*.af; 4574402 results.
12. EMBASE; medication.af; 269026 results.
13. EMBASE; medicines.af; 74542 results.
14. EMBASE; drug*.af; 8398383 results.
15. EMBASE; 10 OR 11 OR 12 OR 13 OR 14; 12503644 results.
16. EMBASE; 9 AND 15; 42 results.
17. EMBASE; 16 [Limit to: Human and Publication Year 2012-2016 and (Human Age Groups Adult 18 to 64 years or Aged 65+ years)]; 17 results.

Medline
1. Medline; clofarabine.af; 369 results.
2. Medline; evoltra.af; 2 results.
3. Medline; clolar.af; 2 results.
4. Medline; 1 OR 2 OR 3; 369 results.
5. Medline; exp LEUKEMIA, MYELOID, ACUTE/; 47093 results.
6. Medline; LEUKEMIA, MYELOID/; 22333 results.
7. Medline; 5 OR 6; 66702 results.
8. Medline; relapsed.af; 27339 results.
9. Medline; refractory.af; 96755 results.
10. Medline; 8 OR 9; 117078 results.
11. Medline; 4 AND 7 AND 10; 53 results.
12. Medline; treatment*.af; 3897689 results.
14. Medline; medication.af; 181235 results.
15. Medline; medicine.af; 25765851 results.
17. Medline; 12 OR 13 OR 14 OR 15 OR 16; 4658833 results.
18. Medline; 11 AND 17; 42 results.
19. Medline; 11 [Limit to: Publication Year 2012-2016 and (Age group Young Adult or Adult or Middle aged or Aged or Aged, 80 and over) and Humans]; 22 results.

Clofarabine in refractory or relapsed AML UKMi final
Cochrane Library
#1 clofarabine
#2 evoltra
#3 clolar
#4 #1 or #2 or #3
#5 "acute myeloid leuk*mia"
#6 "acute myelogenous leuk*mia"
#7 "acute non*lymphocytic leuk*mia"
#8 "acute granulocytic"
#9 #5 or #6 or #7 or #8
#10 relapsed
#11 refractory
#12 #10 or #11
#13 #4 and #9 and #12

Other non-bibliographic databases: clofarabine, acute myeloid leukaemia, myelogenous leukaemia, lymphocytic leukaemia, myeloblastic leukaemia, aml, nonlymphocytic, non-lymphocytic, acute granulocytic, leukaemia, leukemia

12. Evidence selection

• Total number of publications reviewed: 55

• Total number of publications considered relevant: 13

• Total number of publications selected for inclusion in this briefing: 9
13. References


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