Annals of Hematology (2018) 97:1115–1153
https://doi.org/10.1007/s00277-018-3304-y

REVIEW ARTICLE

Salvage regimens using conventional chemotherapy agents for relapsed/refractory adult AML patients: a systematic literature review

Juan Eduardo Megías-Vericat[1] · David Martínez-Cuadrón[2,3] · Miguel Ángel Sanz[2,3] · Pau Montesinos[2,3]

Received: 16 January 2018 / Accepted: 12 March 2018 / Published online: 21 April 2018

Abstract

Prognosis in relapsed and refractory acute myeloid leukemia (R/R AML) patients is dismal, with no satisfactory and standard salvage chemotherapy regimen. We performed a systematic review in order to analyze the clinical outcomes reported with conventional chemotherapy schemes in adult patients with R/R AML. To have a better understanding of the R/R ground, we included studies in R/R AML adult population at any disease stage (i.e., primary refractory as well as first relapse or beyond). Study selection included a total number of 157 out of 850 records, with a wide variety of schedules. Furthermore, only 24 studies were randomized clinical trials (RCTs), being the majority of the studies retrospective analyses in small cohorts. This review reveals that several intensive regimens (cytarabine + mitoxantrone + etoposide or gemtuzumab, and cytarabine + purine analogue ± antracycline) achieve relatively high complete remission (CR) rates (44 to 59.4%). However, most of these schemes did not obtain substantial CR duration (4.9 to 9.8 months) or overall survival (6.2 to 8.7 months). In unfit/vulnerable patients non-intensive approaches are recommended to control disease progression and minimize treatment-related mortality. A better knowledge of the prognostic factors, more effective and less toxic combinations using conventional and new therapies, as well as improvements in allo-HSCT procedure and timing, could play a role to improve the clinical outcomes in the future. Clinical trials should be the first treatment option in R/R AML, both in fit and unfit patients.

Keywords Acute myeloid leukemia · Relapse · Refractory · Salvage therapy · Systematic review

Introduction

Although 60–80% of acute myeloid leukemia (AML) adult patients achieve complete remission (CR) after the first induction chemotherapy, roughly 20% will show primary refractory disease and more than 50% will relapse [1, 2]. Despite salvage treatment, the clinical outcomes of these patients are poor, but acceptable survival rates are achievable depending on prognostic factors and intensity of treatment. The goal of salvage therapy is to achieve a CR in order to perform an allogeneic hematopoietic stem cell transplant (allo-HSCT), which appears to be the most curative therapy in this setting [1]. However, many patients will not proceed to allo-HSCT because of salvage therapy failure or because of inadequate fitness for this procedure. Furthermore, many frail patients will not receive an intensive chemotherapy with a curative intention, enabling the use of non-intensive approaches.

Information about therapy, outcomes, and prognostic factors in the relapsed/refractory (R/R) setting is derived from phase 1 to 3 clinical trials (the latter are very scarce) or from collaborative group registries and protocols, and no standard salvage treatment is established to obtain CR after resistance or relapse [2–13]. It is generally accepted that the enrollment in clinical trials using novel therapies could be the best option in this setting, although the efficacy of these treatments remains unclear, still under evaluation, and non-available for the vast majority of R/R AML patients. The aim of this study is to perform a systematic review of the literature to analyze

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00277-018-3304-y) contains supplementary material, which is available to authorized users.

✉ Pau Montesinos
montesinos_pau@gva.es

[1] Servicio de Farmacia, Área del Medicamento, Hospital Universitari i Politècnic La Fe, Av. Fernando Abril Martorell, 106, 46026 Valencia, Spain

[2] Servicio de Hematología y Hemoterapia, Hospital Universitari i Politècnic La Fe, Av. Fernando Abril Martorell, 106, 46026 Valencia, Spain

[3] CIBERONC, Instituto Carlos III, Madrid, Spain

the clinical outcomes reported with all the available conventional chemotherapy regimens in adult patients with R/R AML.

Materials and methods

Search strategy and selection of studies

This systematic review was conducted and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines [14] by two independent authors (JMV and PM).

We searched the following databases without restrictions: MEDLINE, Cochrane Central Register, EMBASE, Web of Science and Database of Abstracts of Reviews of Effects (DARE), ProQuest Medical Library, and EBSCOhost Online Research Databases. We also hand searched the reference lists of important studies and reviews. The literature last search was on 2 May 2017.

Similar keywords were used in different databases: "acute myeloid leukemia" and relapse (or recurrence or recrudescence or resistance or "salvage therapy" or "salvage treatment") and "Clinical Trial" [Publication Type] not "acute promyelocytic leukemia" not "Clinical Trial, Phase I" [Publication Type].

Study selection was conducted by both authors independently. In case of disagreement, a third reviewer (DMC) decided. Studies that fulfilled the following criteria were included: (1) AML studies using conventional chemotherapy agents for R/R adult AML patients, (2) studies evaluating one or more salvage therapies individually, and (3) studies including effectiveness variables, at least complete remission (CR) rate. Studies that included patients with promyelocytic leukemias and exclusively pediatric or elderly patients were excluded. Furthermore, studies performed in targeted therapy/small molecules cohorts and studies including donor lymphocyte infusions were excluded.

Data extraction

The following data was extracted (summarized in Tables 1, 2, 3, 4, 5, and 6): study design, chemotherapy schedule, AML status (especially the number of R/R patients included), median age, clinical response, and survival rates. The induction outcomes collected were as follows: CR and early death (ED). The CR rate reported for each study summarized in one term the CR rate reported in the study, as well as the CR with incomplete blood count recovery (CRi) and CR without platelet recovery (CRp), because CRi and/or CRp were only reported separately in 21 of the last studies. The CR rates of the subgroups of relapsed, refractory, early relapse (ER) in patients with first CR (CR1) ≤ 6–12 months, late relapse (LR) in patients with > 1 year of CR1, second or beyond relapse or refractory relapse (≥2ndR), and relapse after HSCT, were calculated when this data was provided by the primary sources. We included in the ED rate the cases of induction death, aplastic death, and toxic death reported in a reduced number of studies. The survival rates included were overall survival (OS), disease-free survival (DFS), event-free survival (EFS), and relapse-free survival (RFS). The median OS (mOS) and CR durations (mCRD) were reported in months, and they were estimated in months in the cases that they were reported in days (1 month = 30 days) or weeks (1 month = 4.3 weeks). To better describe the reported series, we showed in the "Results" section the weighted mean and the ranges of CR (wmCR), mOS (wmOS), and mCRD (wmCRD) of different studies adjusted by the sample size, unless more than four studies analyzed the same regimen outcomes.The weighted mean was calculated by summing the product of each variable by its sample size of the different studies and dividing the result by the sum of all the sample sizes. Furthermore, we have represented the CR rates and mOS obtained with the different salvage therapies with boxplot diagrams when we have data from at least four studies (IBM SPSS Statistics version 22, IBM Corp., Chicago, IL, USA). The frequency of allogeneic or autologous HSCT after salvage regimen was also extracted. The studies with less than 40 patients are not shown in Tables 1, 2, 3, 4, 5, and 6, with the exception of the schemes with less than three published studies which were maintained in the tables. The full versions of Tables 1, 2, 3, 4, 5, and 6 were included in the Supplemental Material (Supplemental Tables 1–6).

Results

Systematic search obtained 783 citations from databases and journals and 67 records identified through other sources (Fig. 1). Of the 190 citations selected for full reading, only 157 fulfilled the inclusion criteria and were included (all in English). Reviewers showed an excellent agreement in study selection (kappa = 0.91). The differences in CR and mOS between the main salvage therapies could be visualized with boxplot diagrams in the Figs. 2 and 3.

Cytarabine monotherapy regimens

Eleven of the selected citations included Ara-C monotherapies with intermediate or high doses (from 500 mg/m^2 to 3 g/m^2 every 12 h) in the schedules analyzed (Table 1) [8, 15–24], frequently employed as a comparator of new schemes in randomized clinical trials (CFTs). The results observed in these cohorts were wmCR rate of 23.1% (range 12–32%), wmCRD of 6.3 months (range 0.9 to 11.9), and wmOS 5.8 months (range 3.6 to 8) only reported in 6 studies [16, 18–22]. We

Table 1 Studies of intensive salvage therapy with cytarabine in monotherapy in relapse or refractory AML patients

Study, year	Design	Chemotherapy scheme	*N* (R/RF)	Age, median (range)	Induction outcome [*n* (%)]	Median CRD	Median OS	Other survival outcomes	HSCT rate after salvage therapy
Herzig et al. 1985 [15]	Non-RCT, RETROSP, MC, 2-Arms (see Table 2)	Ara-C (3 g/m^2/12 h d:1–6)	34 (19 R, 15 RF)	37 (16–60)	CR: 15 (47) In RF, CR: 3 (20) In R, CR: 12 (63) ED: 5 (15)	5 m	NA	NA	NA
Capizzi et al. 1988 [16]	RCT, Phase III, MC, 2-Arms (see Table 5)	Ara-C (3 g/m^2/12 h d:1–2; 8–9; 15–16[a])	100 (67 R, 33 RF)	52 (NA), in both arms	CR: 24 (24) In RF, CR: 4 (12) In R, CR: 20 (30) ED: 39 (39)	4.9 m In RF, 3.1 m	In < 60 y, 3.6 m	NA	None
Estey et al. 1993 [17]	Non-RCT, RETROSP, UC, 1-Arm	Ara-C (500 mg/m^2/12 h 9 to 25 doses)	43 (25 ER-RF, 18 LR)	47 (21–78)	CR: 10 (23) ER-RF, CR: 4 (16) LR, CR: 6 (33) ED: 5 (12)	9.1 m	NA	NA	2 (5) auto-HSCT
Estey et al. 1993 [8]	Non-RCT, PROSP/RETROSP, Phase II, UC, 2-Arms (see Table 4)	Ara-C (3 g/m^2/12 h 2 to 6 days) Or Ara-C (500 mg/m^2/12 h 4.5 to 12.5 days). Historical cohorts	77 (54 ER-RF, 29 LR) 44 (26 ER-RF, 18 LR)	NA	CR: 18 (23) ER-RF, CR: 9 (17) LR, CR: 9 (39) CR: 11 (25) ER-RF, CR: 5 (19) LR, CR: 6 (33)	5.1 m 9.1 m	NA	NA	None
Vogler et al. 1994 [18]	RCT, Phase III, MC, 2-Arms (see Table 5)	Ara-C (3 g/m^2/12 h d:1–6)	67 (26 ER, 21 LR, 15 RF)	NA	CR: 21 (31) In RF, CR: 2 (17) In R, CR: 19 (40) ER, CR: 11 (42) LR, CR: 8 (38)	11.9 m	3.7 m	DFS at 5 y: 6%	NA
Karanes et al. 1999 [19]	RCT, Phase III, MC, 2-Arms (see Table 2)	Ara-C (3 g/m^2/12 h d:1–6)	81 (54 R, 27 RF)	48 (14–75)	CR: 26 (32)	9 m	8 m	NA	2 (3) HSCT
Giles et al. 2009 [20]	RCT, Phase III, MC, double-blinded, 2-Arms (see Table 5)	Ara-C (1.5 g/m^2 d:1–3) + placebo	86 (all 1st R)	60 (25–84)	CR: 16 (19) ED: 2 (2)	NA	5.8 m	mPFS 1.1 m	13 (15) allo-HSCT
Faderl et al. 2012 [21]	RCT, Phase III, MC, double-blinded, 2-Arms (see Table 4)	Ara-C (1 g/m^2 d:1–5) + placebo	158 (69 R, 88 RF)	67 (55–86)	CR: 36 (23) ED 30 d: 8 (5)	3.8 m	6.3 m	EFS at 4 m: 17%	30 (19) HSCT
Ravandi et al. 2015 [22]	RCT, Phase III, MC, double-blinded, 2-Arms (see Table 5)	Ara-C (1 g/m^2 d:1–5) + placebo	355 (129 ER, 77 LR, 149 RF)	63 (18–82)	CR: 66 (19) In RF, CR: 18 (12) In R, CR: 48 (24) ER, CR: 20 (16) LR, CR: 28 (36) ED 30d: 23 (7) ED 60d: 68 (19)	NA	6.1 m	NA	103 (29) allo-HSCT

OS and CR has been estimated in months in the cases that it was reported in days (1 month = 30 days) and weeks (1 month = 4.3 weeks). References [23, 24] are not showed of Table 1 because the total number of R/R AML patients were less than 40. The full version of Table 1 is included in the Supplemental Material as Supplemental Table 1

$\geq 2^{nd}$ *R* second or beyond relapse, *AML* acute myeloid leukemia, *Ara-C* cytarabine, *ASNase* asparraginase, *CI* continuous infusion, *CML-BP* chronic myeloid leukemia in myeloid blast phase, *CR* complete remission, *d* days, *ED* early death, *EFS* event-free survival, *ER* early relapse, *HSCT* hematopoietic stem cell transplantation, *LR* late relapse, *m* months, *MC* multicenter, *mCRD* median CR duration, *mDFS* median disease-free survival, *MDS* myelodysplastic syndrome, *mOS* median overall survival, *mPFS* median progression-free survival, *N* population of relapsed/refractory patients with AML, *NA* not available, *OS* overall survival, *PP* poor prognosis, *PROSP* prospective study, *R* relapse, *RCT* randomized clinical trial, *RETROSP* retrospective study, *RF* refractory, *UC* unicentric or single center, *y* year

[a] A third course was begun on day 15 if patients had persistent blasts, i.e., between 5 and 25% blasts in the day 14 marrow

Table 2 Studies of intensive salvage therapy with anthracycline plus cytarabine-based regimens in relapse or refractory AML patients

Study, year	Design	Chemotherapy scheme	*N* (R/RF)	Age, median (range)	Induction outcome [*n* (%)]	Median CRD	Median OS	Other survival outcomes	HSCT rate after salvage therapy
Ara-C + mitoxantrone regimens									
Hiddemann et al. 1987 [25]	Non-RCT, Phase I/II, MC, 1-Arm	Ara-C (3 g/m^2/12 h d:1–4) + MITO (12 mg/m^2 d:3–5) or (10 mg/m^2 d:2–5 or 2–6)	40 (13 ER, 8 LR, 10 RF, 9 ≥ 2ndR)	45 (18–66)	CR: 21 (53) In RF, CR: 1 (10) In R, CR: 20 (67) ER, CR: 9 (69) LR, CR: 3 (38) In ≥2ndR, CR: 8 (89) ED: 13 (33)	4.5 m	3 m	NA	2 (5) allo-HSCT
Walters et al. 1988 [26]	Non-RCT, UC, 1-Arm	Ara-C (3 g/m^2/12 h d:1–3) + MITO (5 mg/m^2 d:1–5) *1 or 2 courses	44 (20 R, 9 RF, 15 ≥ 2ndR)	44 (17–73)	CR: 16 (36) ED: 12 (27)	8 m	4 m	NA	3 (7) HSCT
Martiat et al. 1990 [27]	RCT, MC, 2-Arms (see below in this table)	Ara-C (3 g/m^2 d:1–5) + MITO (7 mg/m^2 (or 5 mg/m^2 if > 60 y) d:1–5)	26 (15 R, 11 RF)	51 (14–71)	CR: 15 (58) In RF, CR: 6 (54) In R, CR: 9 (60)	12 m	12 m	NA	5 (19) allo-HSCT (excluded in OS)
Paciucci et al. 1990 [28]	Non-RCT, MC, 1-Arm	Ara-C (500 mg/m^2/12 h d:1–2 or 1–3) + MITO (5 mg/m^2/12 h d:1–2 or 1–3)	44 (16 R, 14 RF, 14 ≥2ndR)	53 (21–75)	CR: 14 (32) In RF, CR: 4 (29) In R, CR: 7 (44) In ≥2ndR, CR: 3 (21)	4 m	NA	NA	2 (5) auto-HSCT
Hiddermann et al. 1993 [29]	RCT, age-adjusted, MC, 4-Arms	S-HAM: Ara C + MITO	151	NA	CR: 72 (48) ED: 41 (27)	4.5 m	5 m	NA	9 (6) HSCT
		<60 years Ara C (3 g/m^2/12h d:1-2, 8-9) or (1 g/m^2/12h d:1-2, 8-9) + MITO (10 mg/m^2 d:3-4, 10-11)	<60 y: 108 54 Ara C 3 g 54 Ara C 1 g		<60 y; Ara C 3 g CR: 28 (52) ED: 20 (37)				
		≥60 years Ara C (1 g/m^2/12h d:1-2, 8-9) or (0.5 g/m^2/12h d:1-2, 8-9) + MITO (10 mg/m^2 d:3-4, 10-11)	≥60 y: 43 21 Ara C 1 g 22 Ara C 0.5 g		<60 y; Ara C 1 g CR: 24 (44) ED: 8 (15) ≥60 y; Ara C 1 g CR: 10 (48) ED: 8 (38) ≥60 y; Ara C 0.5 g CR: 10 (45) ED: 5 (23)				
Kern et al. 1998 [5]	RCT, age-adjusted, Phase III, MC, 4-Arms	S-HAM: Ara C + MITO <60 years; Ara C 3 g	186 (159 R, 27 RF)	50 (18-75)	CR: 88 (47) ED: 49 (26)	2.9 m	4.2 m	mDFS 5.3 m	NA
		Ara C (3 g/m^2/12h d:1-2, 8-9) + MITO (10 mg/m^2 d:3-4, 10-11)	73		CR: 38 (52) ED: 23 (32)				
		<60 years; Ara C 1 g Ara C (1 g/m^2/12h d:1-2, 8-9) + MITO (10 mg/m^2 d:3-4, 10-11)	65 25		CR: 29 (45) ED: 11 (17)	2.4 m	5.3 m	mDFS 3.3 m	
		≥60 years; Ara C 1 g Ara C (1 g/m^2/12h d:1-2, 8-9) + MITO (10 mg/m^2 d:3-4, 10-11)	23		CR: 11 (44) ED: 9 (36)				
		≥60 y; Ara C 0.5g Ara C (0.5 g/m^2/12h d:1-2, 8-9) +MITO (10 mg/m^2 d:3-4, 10-11)			CR: 10 (43) ED: 6 (26)				

Table 2 (continued)

Study, year	Design	Chemotherapy scheme	*N* (R/RF)	Age, median (range)	Induction outcome [*n* (%)]	Median CRD	Median OS	Other survival outcomes	HSCT rate after salvage therapy
Karanes et al. 1999 [19]	RCT, Phase III, MC, 2-Arms (see Table 1)	Ara-C (3 g/m^2/12 h d:1–6) + MITO (10 mg/m^2 d:7–9)	81 (52R, 29RF)	53 (18–76)	CR: 36 (44)	5 m	6 m	NA	12 (15) HSCT
Sternberg et al. 2000 [4]	Non-RCT, PROSP, Phase II, UC, 1-Arm	Ara-C (0.5 g/m^2/12 h d:1–6) + MITO (5 mg/m^2 d:1–5)	47 (38 R, 2 RF, 7 ≥ 2ndR, 6 SEC)	60 (21–79)	CR: 29 (62) < 60 y, CR: 10 (45) ≥ 60 y, CR: 19 (76)	3.7 m 3.7 m 3.8 m	6 m < 60 y, 3 m ≥ 60 y, 9 m	NA	NA
Ara-C + daunorubicin regimens									
Herzig et al. 1985 [15]	Non-RCT, RETROSP, MC, 2-Arms (see Table 1)	Ara-C (3 g/m^2/12 h d:1–6) + DOX or DNR (20 mg/m^2 or 30 mg/m^2 d:7–9)	44 (17R, 27 RF)	37 (12–72)	CR: 26 (59) In RF, CR: 15 (56) In R, CR: 11 (65) ED: 5 (11)	5 m	NA	NA	NA
List et al. 2001 [30]	RCT, MC, 2-Arms	Ara C (3 g/m^2 d:1-5) + DNR (45 mg/m^2 d:6-8)	107	53	CR: 35 (33) ED: 3 (3)	NA	OS at 2 y: 12%	RFS at 2 y: 9%	9 (17) HSCT
		or	(61 R, 17 RF, 7 ≥2ndR, 22 SEC)	54	CR: 47 (39)		OS at 2 y: 22%	RFS at 2 y: 34%	17 (32) HSCT
		Ara C (3 g/m^2 d:1-5) + DNR (45 mg/m^2 d:6-8) + CsA (6 mg/kg/2h d:6; 4 mg/kg/6h d:6; 16 mg/kg d:6-8)	119 (71 R, 15 RF, 6 ≥2ndR, 27 SEC)		ED: 3 (3)				
Ara C + AMSACRINE regimens									
Martiat et al. 1990 [27]	RCT, MC, 2-Arms (see above in this table)	Ara-C (3 g/m^2 d:1–5) + AMSA (120 mg/m^2 (or 90 mg/m^2 if > 60 y) d:1–5)	26 (19 R, 7 RF)	49.5 (26–67)	CR: 12 (46) In RF, CR: 6 (54) In R, CR: 10 (53)	11 m	8 m	NA	None
Tavernier et al. 2003 [7]	Non-RCT, PROSP, UC, 1-Arm	Ara-C (3 g/m^2/12 h d:1–4) + AMSA (100 mg/m^2 d:5–7)	91 (91 RF)	44 1(16–75)	CR: 45 (49) ED: 11 (12)	NA	7.5 m	mDFS 11.5 m	19 (21) allo-HSCT
Ara-C + idarubicin regimens									
De la Serna et al. 1997 [31]	Non-RCT, PROSP, MC, 1-Arm	Ara-C (1 g/m^2/12 h d:1–4) + IDA (12 mg/m^2 d:1–3)	61 (ER 10, LR 28, 23 RF)	NA (Adults)	CR: 33 (54) In RF, CR: 12 (52) In R, CR: 21 (55) ER, CR: 2 (20) LR, 19 (68) ED: 6 (10)	9 m In R, 9 m In RF, 10 m ER, 8 m LR, 9 m	8 m In R, 9 m In RF, 7 m ER, 8 m LR, 12 m	NA	10 (16) HSCT, 7 auto-HSCT and 3 allo-HSCT
Fiegl et al. 2014 [32]	RCT, Phase II, MC, 2-Arms (see Table 4)	SHAI: Ara-C (1 g*/m^2/12 h d:1–2, 8–9) + IDA (10 mg/m^2 d:3–4, 10–11)* Ara-C (3 g/m^2/12 h) in ≤60 y with RF or ≥ 2R	139 (R or RF)	57 (17–83)	CR: 59 (42) ED: 28 (20)	2 m	5.8 m	mDFS 3.9 m	36 (26) HSCT, 33 allo-HSCT and 3 auto-HSCT
Ara-C + aclarubicin regimens									
Saito et al. 2000 [33]	Non-RCT, PROSP, Phase II, UC, 1-Arm	CAG: Ara-C (10 mg/m^2/12 h SC d:1–14) + ACLA (14 mg/m^2 d:1–4), G-CSF (200 μg/m^2/d d:1–14)	43 (5 ER, 18 LR, 8 RF, 12 ≥ 2ndR)	51 (15–82)[a]	CR: 30 (70) In RF, CR: 1 (13) In R, CR: 29 (83) ER, CR: 3 (60) LR, CR: 17 (94) In ≥2ndR, 9 (75)	NA	In R, 15 m In R, OS at 5 y: 30%	In R, mDFS 8 m In R, DFS at 5 y: 15%	NA
			114		CR: 58 (51)	NA		NA	30 (26) allo-HSCT

Table 2 (continued)

Study, year	Design	Chemotherapy scheme	*N* (R/RF)	Age, median (range)	Induction outcome [*n* (%)]	Median CRD	Median OS	Other survival outcomes	HSCT rate after salvage therapy
Zhang et al. 2013 [34]	RCT, MC, 2-Arms (see Table 3)	CAG: Ara-C (10 mg/m^2/12 h SC d:1–14) + ACLA (14 mg/m^2 d:1–4), G-CSF (200 μg/m^2/d d:0–14)		Mean: 59 (± 51.8)	ED: 8 (7)		OS at 5 y: 24%		
Ara-C + liposomal daunorubicin regimens									
Cortes et al. 2001 [35]	Non-RCT, PROSP, Phase I/II, UC, 1-Arm	Ara-C (1 g/m^2 d:1–4 or d:1–3 in > 60 y) + DNX (75 or 100 or 125 or 135 or 150 mg/m^{2}d:1–3)	62 (47 R, 15 RF)	61 (21–79)	CR: 18 (29)	15.3 m	7 m OS at 1 y: 28%	NA	7 (11) allo-HSCT
Litzow et al. 2010 [36]	RCT, Phase II, MC, 2-Arms (see Table 5)	Ara-C (1 g/m^2 d:1–4) + DNX (135 mg/m^2 d:1–3)	29 (19 R, 10 RF)	52 (27–85)	CR: 2 (7)	NA	2.4 m	NA	NA
CPX-351 (liposome-encapsulated fixed-molar-ratio formulation of Ara-C + DNR)									
Cortes et al. 2015 [37]	RCT, Phase II, MC, 2-Arms	CPX-351 (100 units/m^2 d: 1, 3, 5)	81 (81 R)	52	CR: 40 (49) ED 30d: 6 (7)	NA	8.5 m	mEFS 4 m	38 (47) HSCT
		or			ED 60d: 12 (15)	NA	OS at 1 y: 36%	mEFS 1.5 m	21 (48) HSCT
		Other salvage regimens:	44 (44 R)	56	ED 90d: 15 (19)		6.3 m OS at 1 y: 27%		
		Ara C + MITO + ETOP (23 pts), Ara C + IDA (8 pts), other (13 pts)			CR: 18 (41) ED 30d: 2 (5) ED 60d: 7 (16) ED 90d: 13 (30)				
Ara C + anthracyclines (not defined)									
Hospital et al. 2014 [38]	Non-RCT, RETROSP, MC, 2-Arms (see tables 3 & 5)	Ara C (high [53 pts] or standard dose [44 pts]) + anthracycline	97 CBF-AML at R	42 (16-74)	CR: 85 (88) ED: 1 (1)	NA	OS at 5 y: 44%	DFS at 5 y: 42%	55 (57) HSCT, 50 allo-HSCT & 15 auto-HSCT

OS and CR has been estimated in months in the cases that it was reported in days (1 month = 30 days) and weeks (1 month = 4.3 weeks). References [39–57] are not showed of Table 2 because the total number of R/R AML patients were less than 40. The full version of Table 2 is included in the Supplemental Material as Supplemental Table 2

≥2^{nd} *R* second or beyond relapse, *ACLA* aclarubicin, *AL* acute leukemia, *ALL* acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *AMSA* amsacrine, *ANLL* acute non-lymphocytic leukemia, *Ara-C* cytarabine, *CBF-AML* core-binding factor-acute myeloid leukemia, *CI* continuous infusion, *CML-BP* chronic myeloid leukemia in myeloid blast phase, *CR* complete remission, *CsA* cyclosporine, *d* days, *DNR* daunorubicin, *DNX* liposomal daunorubicin, *DOX* doxorubicin, *ED* early death, *EFS* event-free survival, *ETOP* etoposide, *G-CSF* granulocyte colony-stimulating factor, *HSCT* hematopoietic stem cell transplantation, *IDA* idarubicin, *m* months, *mCRD* median CR duration, *mDFS* median disease-free survival, *MDS* myelodysplastic syndrome, *MITO* mitoxantrone, *mOS* median overall survival, *MC* multicenter, *N* population of relapsed/refractory patients with AML, *NA* not available, *NR* not reached, *OS* overall survival, *PP* poor prognosis, *PROSP* prospective study, *pts* patients, *R* relapse, *RCT* randomized clinical trial, *RETROSP* retrospective study, *RF* refractory, *RFS* relapse-free survival, *SC* subcutaneous, *SEC* secondary AML, *t(8;21)* translocation (8;21), *UC* unicentric or single center, *UT* untreated, *w* weeks, *WBC* white blood cells, *y* year

[a] Results of the entire 69 poor-risk AML cohort, including 43 R-RF AML and 26 UT AML

Table 3 Studies of salvage therapy with anthracycline plus cytarabine plus third-agent based regimens in relapse or refractory AML patients

Study, year	Design	Chemotherapy scheme	*N* (R/RF)	Age, median (range)	Induction outcome [*n* (%)]	Median CRD	Median OS	Other survival outcomes	HSCT rate after salvage therapy
Ara-C + MITO + ETOP regimens									
Spadea et al. 1993 [58]	Non-RCT, RETROSP, Phase II, UC, 1-Arm	Ara-C (1 g/m^2 d:1–6) + MITO (6 mg/m^2 d:1–6) + ETOP (80 mg/m^2 d: 1–6)	58 (5 ER, 15 LR, 10 R HSCT, 28 RF)	36.7 (4.5–60.6)[a]	CR: 41 (55) In RF, CR: 11 (39) In R, CR: 23 (77) ER, CR: 3 (60) LR, CR: 14 (92) In R HSCT, 6 (60) ED: 7 (10)	9 m	NA	mEFS 8 m EFS at 20 m: 19%	NA
Archimbaud et al. 1993 [59]	Non-RCT, PROSP/RETROSP, MC, 2-Arm	Ara C (500 mg/m^2 d:1-3, 8-10) + MITO (12 mg/m^2 d:1-3) + ETOP (200 mg/m^2 d: 8-10) + GM-CSF (5 μg/kg d:4-8)	20 (14 R, 3 RF, 3 ≥2ndR)	43 (20-60)	CR: 6 (30) In RF, CR: 0 (0) In R, CR: 4 (29) In ≥2ndR, CR: 2 (66)	NA	2.1 m	mDFS 1.1 m	NA
		or Ara C (500 mg/m^2 d:1-3, 8-10) + MITO (12 mg/m^2 d:1-3) + ETOP (200 mg/m^2 d: 8-10). Historical cohort	38 (23 R, 12 RF, 3 ≥2ndR)	41 (16-60)	ED: 3 (15) CR: 16 (43) In RF, CR: 3 (25) In R, CR: 12 (52) In ≥2ndR, CR: 1 (33) ED: 3 (8)		4.3 m	mDFS 3.5 m	
Ohno et al. 1994 [60]	RCT, Phase III, MC, double-blinded, 2-Arms	Ara C (200 mg/m^2 d:1-7) + MITO (7 mg/m^2 d:1-3) + ETOP (100 mg/m^2 d:1-5) + G-CSF (200 μg/m^2 d:-1-33)	24 (19 R, 3 RF, 2 ≥2ndR)	43 (18-63)	CR: 13 (54) ED: 0 (0)	NA	NA	NA	NA
		or Ara C (200 mg/m^2 d:1-7) + MITO (7 mg/m^2 d:1-3) + ETOP (100 mg/m^2 d:1-5) + placebo	26 (16 R, 3 RF, 7 ≥2ndR)	47 (16-66)	CR: 11 (42) ED: 2 (8)				
Archimbaud et al 1995 [61]	Non-RCT, PROSP, MC, 2-Arm	EMA-86: Ara-C (500 mg/m^2 d:1–3, 8–10) + MITO (12 mg/m^2 d:1–3) + ETOP (200 mg/m^2 d: 8–10)* 1–2 courses	133 (39 ER, 63 LR, 22 RF, 9 ≥ 2ndR)	43 (15–70)	CR: 79 (60) In RF, CR: 9 (41) In R, CR: 66 (65) ER, CR: 18 (46) LR, CR: 48 (76) In ≥2ndR, CR: 4 (45) ED: 15 (11)	NA	In LR, OS at 5 y: 20% In RF, OS at 5 y: 3%	In LR, DFS at 5 y: 25% In RF, DFS at 5 y: 12%	25 (19) HSCT, 12 allo-HSCT and 13 auto-HSCT
Vignetti et al 1996 [62]	Non-RCT, PROSP, Phase II, UC, 1-Arm	MEC: Ara-C (1 g/m^2 d:1–6) + MITO (6 mg/m^2 d:1–6) + ETOP (80 mg/m^2 d: 1–6)	50 (50 R)	37 (4–69)	CR: 34 (68) ED: 3 (6)	12 m	OS at 6 y: 29%	DFS at 6 y: 29% EFS at 6 y: 19%	16 (32) HSCT, 15 auto-HSCT and 1 allo-HSCT
Thomas et al. 1999 [63]	RCT, Phase III, MC, double-blinded, 2-Arms	EMA-94: Ara C (500 mg/m^2 d:1-3, 8-10) + MITO (12 mg/m^2 d:1-3) + ETOP (200 mg/m^2 d: 8-10) + GM-CSF (5 μg/kg d:4-8)* 1-2 courses	95 (36 R, 59 RF)	47 (17-65)	CR: 62 (65) In RF, CR: 30 (51) In R, CR: 32 (89) ED: 5 (5)	5.1 m	10.1 m	mDFS 8.4 m	18 (19) HSCT, 9 allo-HSCT & 9 auto-HSCT
		or							

Table 3 (continued)

Study, year	Design	Chemotherapy scheme	*N* (R/RF)	Age, median (range)	Induction outcome [*n* (%)]	Median CRD	Median OS	Other survival outcomes	HSCT rate after salvage therapy
		Ara C (500 mg/m^2 d:1-3, 8-10) + MITO (12 mg/m^2 d:1-3) + ETOP (200 mg/m^2 d: 8-10)+ placebo * 1-2 courses	97 (36 R, 61 RF)	46 (16-65)	CR: 57 (59) In RF, CR: 28 (46) In R, CR: 29 (81) ED: 8 (8)	3.8 m	8.5 m	mDFS 8 m	14 (14) HSCT, 9 allo-HSCT & 5 auto-HSCT
Revesz et al. 2003 [64]	Non-RCT, RETROSP, UC, 1-Arm	EMA: Ara-C (500 mg/m^2 d:1–3, 8–10) + MITO (12 mg/m^2 d:1–3) + ETOP (200 mg/m^2 d: 8–10) ± GM-CSF (5 μg/kg d:4–8)* 1–2 courses	66 (66 RF)	48 (16–79)	CR: 24 (36) ED: 4 (6)	NA	5 m	mDFS 4.9 m	6 (9) HSCT, 5 allo-HSCT and 1 auto-HSCT
Lee et al. 2009 [65]	Non-RCT, PROSP, Phase II, UC, 2-Arms	Ara C (1 g/m^2/24h CI d:1-5) + MITO (12 mg/m^2 d:1-3) + ETOP (150 mg/m^2 d: 1-3)* 1-2 courses (cohort from Lee 2006 [66])	33 (14 R, 19 RF)	34 (20-59)	CR: 17 (52)	3.9 m	7.3 m OS at 3 y: 6%	NA	4 (12) allo-HSCT
		or							
		CME2: Ara C (1 g/m^2/24h CI d:1-5) + MITO (36 mg/m^2 d:1) + ETOP (150 mg/m^2 d: 1-3)* 1-2 courses	25 (19 R, 6 RF)	44 (19-68)	CR: 6 (24)	3.7 m	3.7 m		1 (4) allo-HSCT
Price et al. 2011 [67]	Non-RCT, RETROSP, UC, 2-Arms (see Table 4)	MEC: + Ara-C (1 g/m^2 d:1–5) + MITO (8 mg/m^2 d:1–5) + ETOP (100 mg/m^2 d:1–5)	65 (41 R, 24 RF)	55.0 (21–90)	CR: 15 (24) In RF, CR: 4 (22) In R, CR: 7 (26) ED 30d: 7 (11)	3.5 m	4.5 m	NA	12 (18) allo-HSCT
Ara-C + IDA + ETOP regimens									
Carella et al. 1993 [68]	Non-RCT, PROSP, Phase II, MC, 1-Arm	Ara-C (600 mg/m^2 d:1–5) + IDA (6 mg/m^2 d:1–5) + ETOP (150 mg/m^2 d:1–3)	97 (50 R, 36 RF, 8 R HSCT, 3 ≥2ndR)	37 (9–64)	CR: 42 (43) In RF, CR: 10 (28) In R, CR: 25 (50) In ≥2ndR, CR: 3 (100) In R HSCT, CR: 4(50) ED: 11 (11)	3.7 m	2.3 m	NA	7 (7) HSCT, 5 allo-HSCT and 2 auto-HSCT
Ara-C + DNR + ETOP regimens									
Liu Yin et al. 2001 [69]	RCT, MC, 2-Arms	ADE 10+3+5: Ara C (100 mg/m^2/12h d:1-10) + DNR (50 mg/m^2 d: 1, 3, 5) + ETOP (100 mg/m^2 d: 1-5)* 1 course; + ADE 8+3+5 *1-2 courses	85 (40 ER, 24 LR, 21 RF)	48 (4-75)	CR: 46 (54) In RF, CR: 8 (38) In R, CR: 38 (59) ER, CR: 18 (45) LR, CR: 20 (83) ED: 14 (16)	NA	OS at 3 y: 12%	DFS at 3 y: 22%	29 (17) HSCT, 19 allo-HSCT & 10 auto-HSCT
		or							
		Sequencial ADE: Ara C (2 g/m^2/12h d:1-3) + DNR (50 mg/m^2 d: 1-3) + ETOP (200 mg/m^2 d:8-10)*1,2 courses	85 (42 ER, 25 LR, 18 RF)		CR: 28 (33) In RF, CR: 6 (33) In R, CR: 22 (34) ER, CR: 10 (24) LR, CR: 13 (52) ED: 20 (24)		OS at 3 y: 6 %	DFS at 3 y: 14%	

Table 3 (continued)

Study, year	Design	Chemotherapy scheme	*N* (R/RF)	Age, median (range)	Induction outcome [*n* (%)]	Median CRD	Median OS	Other survival outcomes	HSCT rate after salvage therapy
Milligan et al. 2006 [70]	RCT, MC, 2-Arms (see Table 4)	ADE 10 + 3 + 5: Ara-C (100 mg/m^2/12 h d:1–10) + DNR (50 mg/m^2 d: 1, 3, 5) + ETOP (100 mg/m^2 d: 1–5)* 1 course; + ADE 8 + 3 + 5 *1–2 courses ± G-CSF ± ATRA	126 (58 R, 46 RF)	NA	CR: 79 (63) ED: 6 (5) No impact of G-CSF and ATRA	NA	OS at 4 y: 27% No impact of G-CSF and ATRA	DFS at 4 y: 29% No impact of G-CSF and ATRA	31 (25) HSCT, 22 allo-HSCT, 9 auto-HSCT
Ara-C + AMSA + ETOP regimens									
Sung et al. 2005 [71]	Non-RCT, PROSP, Phase II, UC, 1-Arm	Ara-C (1 g/m2/12 h d:1–3) + AMSA (100 mg/m^2 d:1–3) + ETOP (100 mg/m^2 d: 1–5)	29 (23 R, 6 RF)	35 (15–65)[b]	CR: 13 (45) ED: 5 (17)	NA	5 m[b]	mDFS 1.5 m[b]	11 (38) HSCT, 9 allo-HSCT and 2 auto-HSCT
Ara-C + ACLA + ETOP regimens									
Zhang et al. 2013 [34]	RCT, MC, 2-Arms (see Table 2)	E-CAG: Ara-C (10 mg/m^2/12 h SC d:1–14) + ACLA (14 mg/m^2 d:1–4) + ETOP (30 mg/m^2 d:1–4) G-CSF (200 μg/m^2 d:0–14)	114	Mean: 56 (± 49.1)	CR: 81 (71.1) ED: 8 (7)	NA	OS at 5 y: 27%	NA	33 (29) allo-HSCT
Ara-C + ACLA + DAC regimens									
Song et al. 2012 [72]	Non-RCT, PROSP, UC, 1-Arm	Ara-C (100 mg/m^2 d:1–5) + ACLA (12 mg/m^2 d: 1–5) + DAC (15 mg/m^2 d:1–5) *at least 2 courses	9 (3 R, 6 RF)	54 (23–80)	CR: 6 (67) In RF, CR: 5 (83) In R, CR: 1 (33)	NA	7 m	NA	1 (11) allo-HSCT
Ara-C + DOX + vincristine regimens									
Van Prooijen et al. 1984 [73]	Non-RCT, PROSP, UC, 1-Arm	Ara-C (500 mg/m^2/12 h d:3–8) + DOX (50 mg/m^2 d:1) + VINCRISTINE (1 mg/m^2 d:2)	15 ANLL (12 R, 3 RF)	34 (19–74)	CR: 12 (80)	5 m	NA	NA	1 (7) HSCT
Ara-C + MITO + dacarbazine regimens									
Franchi et al. 1992 [74]	Non-RCT, RETROSP, UC, 1-Arm	Ara-C (1 g/m^2 d:8–14) + MITO (6 mg/m^2 d:8–14) + DACARBAZINE (800 mg/m^2 d:0–2, in 2 patients in monotherapy)	9 (3 R, 4 RF, 2 R HSCT)	NA	CR: 4 (44)	NA	4.9 m	NA	NA
Ara-C + MITO + GO regimens									
Chevalier et al. 2008 [75]	Non-RCT, RETROSP, MC, 1-Arm	MIDAM: Ara-C (1 g/m^2/12 h d:1–5) + MITO (12 mg/m^2 d:1–3) + GO (9 mg/m^2 d:4)	62 (44 R, 18 RF)	55.5 (16–71)	CR: 39 (63) ED: 4 (7)	NA	9.5 m OS at 2 y: 41%	mEFS 4.4 m EFS at 2 y: 33%	12 (19) allo-HSCT
Chevalier et al. 2011 [76]	Non-RCT, RETROSP, MC, 1-Arm	MIDAM: Ara-C (1 g/m^2/12 h d:1–5) + MITO (12 mg/m^2 d:1–3) + GO (9 mg/m^2 d:4) 128 pts *Other intensive regimen (Ara-C ± ANT ± ETOP) + GO, 10 pts	138 (25 ER, 56 LR, 57 RF)	55 (19–70)	CR: 88 (64) In RF, CR: 28 (49) In R, CR: 60 (74) ER, CR: 17 (68) LR, CR: 43 (77) ED: 10 (7)	NA	OS at 2 y 36% *Other regimen OS at 2 y: 27%	EFS at 2 y 29% *Other reg EFS at 2 y: 30%	47 (34) allo-HSCT

Table 3 (continued)

Study, year	Design	Chemotherapy scheme	*N* (R/RF)	Age, median (range)	Induction outcome [*n* (%)]	Median CRD	Median OS	Other survival outcomes	HSCT rate after salvage therapy
Hospital et al. 2014 [38]	Non-RCT, RETROSP, MC, 2-Arms (see Tables 2 and 5)	GO (6 to 9 mg/m^2 d:1 or 3 mg/m^2 d:1, 4, 7) + Ara-C ± anthracycline	48 CBF-AML at R	46 (20–76)	CR: 42 (88)	NA	OS at 5 y: 65%	DFS at 5 y: 68%	31 (65) HSCT, 28 allo-HSCT and 3 auto-HSCT
Peterlin et al. 2016 [77]	Non-RCT, RETROSP, UC, 2-Arms	S-MIDAM: Ara C (1 g/m^2/12h d:1-5) + MITO (12 mg/m^2 d:1-3) + GO (9 mg/m^2 d:4)	15 (14 R, 1 RF)	55 (9-70)	CR: 8 (53)	NA	7.2 m	NA	6 (40) allo-HSCT
		or F-MIDAM: Ara C (1 g/m^2/12h d:1-5) + MITO (12 mg/m^2 d:1-3) + GO (3 mg/m^2 d:1, 4, 7)	18 (11 R, 7 RF)	52 (26-70)	CR: 11 (61)		10.2 m		12 (67) allo-HSCT
Hütter-Krönke et al. 2016 [78]	Non-RCT, PROSP, Phase II, MC, 1-Arm	GO-A-HAM: Ara-C (3 g/m^2/12 h d:1–3) + MITO (12 mg/m^2 d:2–3) + GO (3 mg/m^2 d:1) + ATRA oral (45 mg/m^2 d:4–6; 15 mg/m^2 d:7–28)	93 (93 RF)	48 (22–62)	CR: 47 (51) ED: 3 (3)	NA	16 m OS at 4 y: 32%	NA	71 (76) allo-HSCT

OS and CR has been estimated in months in the cases that it was reported in days (1 month = 30 days) and weeks (1 month = 4.3 weeks). References [66, 79–82] are not showed of Table 3 because the total number of R/R AML patients were less than 40. The full version of Table 3 is included in the Supplemental Material as Supplemental Table 3

≥2nd *R* second or beyond relapse, *2-CdA* cladribine, *ACLA* aclarubicin, *AL* acute leukemia, *AML* acute myeloid leukemia, *ANLL* acute non-lymphocytic leukemia, *ANT* anthracycline, *Ara-C* cytarabine, *ATRA* all-trans retinoic acid, *CBF-AML* core-binding factor-acute myeloid leukemia, *CI* continuous infusion, *CR* complete remission, *CsA* cyclosporine, *d* days, *DAC* decitabine, *DNR* daunorubicin, *DNX* liposomal daunorubicin, *DOX* doxorubicin, *ED* early death, *EFS* event-free survival, *ER* early relapse, *ETOP* etoposide, *G-CSF* granulocyte colony-stimulating factor, *GO* gemtuzumab ozogamicin, *HSCT* hematopoietic stem cell transplantation, *LR* late relapse, *m* months, *mD* median duration, *mDFS* median disease-free survival, *MDS* myelodysplastic syndrome, *MITO* mitoxantrone, *mOS* median overall survival, *N* population of relapsed/refractory patients with AML, *NA* not available, *NR* not reached, *OS* overall survival, *PFS* progression-free survival, *pts* patients, *R* relapse, *RCT* randomized clinical trial, *RF* refractory, *RFS* relapse-free survival, *SC* subcutaneous, *SEC* secondary AML, *TOPO* topotecan, *w* weeks, *UT* untreated, *WBC* white blood cells, *y* year

[a] Results of the entire 74 AML poor- risk cohort, including 3 R; 2 RF. 20 R, 28 RF, 16 SEC patients

[b] Results of the entire 51 AML/ALL R/RF cohort, including 29 AML and 21 ALL patients

Table 4 Studies of salvage therapy with purine analogue plus cytarabine-based regimens in relapse or refractory AML patients

Study, year	Design	Chemotherapy scheme	*N* (R/RF)	Age, median (range)	Induction outcome [n (%)]	Median CRD	Median OS	Other survival outcomes	HSCT rate after salvage therapy
Fludarabine + Ara-C regimens ± G-CSF: FLA, FLAG									
Estey et al. 1993 [8]	Non-RCT, PROSP, Phase II, UC, dose-finding, 2-Arms (see Table 1)	Ara-C (1 g/m^2 or 2 g/m^2 or 3 g/m^2 d:1–5) + FLU (30 mg/m^2 d:1–5)	59 (25 R, 9 RF, 25 ≥ 2ndR)	52 (17–76)	CR: 21 (36) In ER-RF, CR: 7 (18) In LR, CR: 14 (70) ED: 6 (10)	9.1 m	NA	NA	HSCT excluded
Jackson et al. 2001 [83]	Non-RCT, PROSP, Phase II, MC, 1-Arm	FLAG: Ara-C (2 g/m^2 d:1–5) + FLU (30 mg/m^2 d:1–5) + G-CSF (300 μg/m^2 d:0–6)	55 (44 ER-RF, 21 LR)	47 (18–74)	CR: 30 (55) In ER-RF, CR: 13 (30) In LR, CR: 17 (81) ED: 9 (16)	NA	In ER-RF 3 m OS at 1 y: 20% In LR 16.2 m OS at 1 y: 67%	In ER-RF mEFS 0 m In LR mEFS 8.2 m	7 (13) HSCT, 4 allo-HSCT and 3 auto-HSCT
Milligan et al. 2006 [70]	RCT, MC, 2-Arms (see Table 3)	FLA: Ara-C (2 g/m^2 d:1–5) + FLU (30 mg/m^2 d:1–5) ± G-CSF ± ATRA	124 (58 R, 41 RF)	NA	CR: 76 (61) ED: 9 (7) No impact of G-CSF and ATRA	NA	OS at 4 y: 16% No impact of G-CSF and ATRA	DFS at 4 y: 23% No impact of G-CSF and ATRA	31 (25) HSCT, 23 allo-HSCT and 8 auto-HSCT
Lee et al. 2009 [84]	Non-RCT, RETROSP, MC, 1-Arm	FLAG: Ara-C (2 g/m^2 d:1–5) + FLU (30 mg/m^2 d:1–5) + G-CSF (5 μg/kg d:0 until WBC > 0.5 × 10^9)	61 (29 R, 18 RF, 6 ≥ 2ndR, 8 R HSCT)	34 (20–70)	CR: 29 (48) In RF, CR: 7 (39) In R, CR: 17 (59) ER, CR: 7 (33) LR, CR: 10 (71) In ≥2ndR, CR: 4 (67) In R HSCT, CR: 1 (13) ED: 7 (11)	17.1 m	14. 3 m OS at 3 y: 30%	NA	6 (10) allo-HSCT
Jabbour et al. 2012 [85]	Non-RCT, PROSP, Phase II, MC, 2-Arms (see below in this table)	Ara-C (0,5 g/m^2/12 h d:1–5) + FLU (15 mg/m^2/12 h d:1–5)* 1–2 courses. If age ≥ 65 y, d:1–4; if PS = 3, d:1–3	48[a] (R-RF)	62 (19–85)[a]	CR: 9 (19)[a]	NA	7.4 m[a] OS at 2 y: 38%[a]	mDFS 1.2 m[a]	NA
Becker et al. 2012 [86]	Non-RCT, PROSP, MC, 3-Arms (see below Becker et al. 2011 [87] in this table)	FLA: Ara-C (2 g/m^2 or 3 g/m^2 d:1–5) + FLU (30 mg/m^2 d:1–5)	81 (36 ER, 25 LR, 20 RF)	56 (18–82)	CR: 22 (27) In RF, CR: 2 (10) In ER, CR: 5 (14) In LR, CR: 15 (60)	NA	3.4 m	NA	NA
		or FLAG: Ara-C (2 g/m^2 or 3 g/m^2 d:1–5) + FLU	20	57 (22–87)	CR: 4 (20) In RF, CR: 0 (0)	NA	3.8 m		

Table 4 (continued)

Study, year	Design	Chemotherapy scheme	*N* (R/RF)	Age, median (range)	Induction outcome [n (%)]	Median CRD	Median OS	Other survival outcomes	HSCT rate after salvage therapy
		(30 mg/m^2 d:1–5) + G-CSF	(12 ER, 5 LR, 3 RF)		In ER, CR: 1 (8) In LR, CR: 3 (60)				
Kim et al. 2016 [88]	Non-RCT, PROSP, Phase II, MC, 2-Arms (see below in this table)	C-FLAG1: Ara-C (1 g/m^2 d:1–2, 200 mg/m^2 d:3–5) + FLU (30 mg/m^2 d:1–5) + G-CSF (400 μg/m^2 d:1–5)	33 (26 R, 7 RF)	66 (60–74)	CR: 15 (45) ED: 0 (0)	4 m in both arms	3.2 m in both arms OS at 1 y and 3 y: 22 and 9% in both arms		2 (6) allo-HSCT
Cladribine + Ara-C regimens ± G-CSF: CLAG									
Wrzesien - Kus et al. 2003 [89]	Non-RCT, PROSP, MC, 1-Arm	CLAG: 2-CdA (5 mg/m^2 d:1–5) + Ara-C (2 g/m^2 d:1–5) + G-CSF (300 μg d:0–5)	58 (8 R, 50 RF)	45 (18–67)	CR: 29 (50) ED: 10 (17)	NA	7.9	mDFS 4 m	6 (10) HSCT, 2 allo-HSCT and 4 auto-HSCT
Price et al. 2011 [67]	Non-RCT, RETROSP, UC, 2-Arms (see Table 3)	CLAG: 2-CdA (5 mg/m^2 d:1–5) + Ara-C (2 g/m^2 d:1–5) + G-CSF (300 μg d:0–5)	97 (53 R, 44 RF)	55 (23–83)	CR: 33 (38) In RF, CR: 15 (46) In R, CR: 14 (37) ED 30d: 9 (9)	6.1 m	7.3 m		25 (26) allo-HSCT
Halpern et al. 2017 [90]	Non-RCT, PROSP -RETROSP, Phase I/II, MC, 2-Arms (see below and in Table 5)	G-CLAC: 2-CdA (15–25 mg/m^2 d:1–5) + Ara-C (2 g/m^2 d:1–5) + G-CSF (5 μg/kg d:0 until neutrophil recovery) RETROSP. COHORT	61 (32 R, 29 RF)	51 (19–91)	CR: 32 (52) ED: 0 (0)	NA	5.2 m	NA	26 (43) allo-HSCT
Fludarabine + Ara-C + idarubicin regimens ± G-CSF: FLAG-IDA									
Pastore et al. 2003 [91]	Non-RCT, RETROSP, UC, 1-Arm	FLAG-IDA: Ara-C (2 g/m^2 d:1–5) + FLU (30 mg/m^2 d:1–5) + IDA (10 mg/m^2 d:1–3) + G-CSF (5 μg/kg d:6 until WBC > 0.5 × 10^9)	46 (30 R, 10 RF, 6 R HSCT)	41 (15–60)	CR: 24 (52) In RF, CR: 5 (50) In R, CR: 19 (53) ED: 3 (7)	NA	11 m	mDFS 12 m	15 (33) HSCT, 11 allo-HSCT and 4 auto-HSCT
Martin et al. 2009 [92]	Non-RCT, RETROSP, UC, 2-Arms (see below in this table)	FLAG-I: Ara-C (2 g/m^2 d:1–5) + FLU (25 mg/m^2 d:1–5) + IDA (12 mg/m^2	23 (16 R, 2 RF, 5 ≥ 2ndR)	48 (18–70)	CR: 12 (52) ED: 8 (35)	16.8 m	8.8 m	mDFS 7.4 m	5 (22) allo-HSCT

Table 4 (continued)

Study, year	Design	Chemotherapy scheme	*N* (R/RF)	Age, median (range)	Induction outcome [n (%)]	Median CRD	Median OS	Other survival outcomes	HSCT rate after salvage therapy
		d:1–3) ± G-CSF (16 patients)							
Montillo et al. 2009 [93]	Non-RCT, RETROSP, UC, 1-Arm	FLAIRG: Ara-C (1 g/m^2/12 h d:1–5) + FLU (15 mg/m^2/12 h d:1–5) + IDA (10 mg/m^2 d: 1–3) + ATRA (45 mg/m^2 oral d:1–10) + G-CSF (5 μg/kg d:0–5, 7- until WBC > 0.5 × 10^9/l for 3 d)	52 (21 R, 31 RF)	46.5 (16–60)	CR: 36 (69) In RF, CR: 22 (70) In R, CR: 14 (67) ED: 4 (8)	55.7 m	12.4 m	mDFS 33.8 m	19 (37) HSCT, 11 allo-HSCT and 8 auto-HSCT
Fiegl et al. 2014 [32]	RCT, Phase II, MC, 2-Arms (see Table 2)	F-SHAI: Ara-C (1 g*/m^2/12 h d:1–2, 8–9) + IDA (10 mg/m^2 d:3–4, 10–11) + FLU (15 mg/m^2 d:1–2, 8–9) * Ara-C (3 g/m^2/12 h) in ≤60 y with RF or ≥ 2ndR	141 (R or RF)	52 (19–76)	CR: 76 (54) ED: 28 (20)	3.4 m	6.7 m	mDFS 5.8 m	52 (37) HSCT, 44 allo-HSCT and 8 auto-HSCT
Kim et al. 2014 [94]	Non-RCT, PROSP, Phase II, MC, 2-Arms	CI-FLAG1-IDA: Ara C (1 g/m^2 CI d:1-5) + FLU (30 mg/m^2 d:1-5) + IDA (12 mg/m^2 d: 1-3) + G-CSF (400 μg/m^2 d:1-5)	38 (29 R, 9 RF)	40 (18-57)	CR: 12 (32)		2.5 m		10 (26) HSCT, 8 allo-HSCT & 2 auto-HSCT
		or CI-FLAG2-IDA: Ara C (1 g/m^2 CI d:1-2, 200 mg/m^2 d:3-5) + FLU (30 mg/m^2 d:1-5) + IDA (6 mg/m^2 d: 1-3) + G-CSF (400 μg/m^2 d:1-5)	68 (46 R, 22 RF)	44 (15-62)	CR: 25 (37)	NA	5.6 m	NA	35 (52) HSCT, 33 allo-HSCT & 2 auto-HSCT
Kim et al. 2016 [88]	Non-RCT, PROSP, Phase II, MC, 2-Arms (see above in this table)	CI-FLAG2-IDA: Ara-C (1 g/m^2 CI d:1–2, 200 mg/m^2 d:3–5) + FLU (30 mg/m^2	68 (30 R, 16 R HSCT, 22 RF)	44 (15–62)	CR: 25 (37) ED: 0 (0)	4 m in both arms	3.2 m in both arms OS at 1 and 3 y: 22 and 9% in both arms	NA	35 (52) HSCT

Table 4 (continued)

Study, year	Design	Chemotherapy scheme	*N* (R/RF)	Age, median (range)	Induction outcome [n (%)]	Median CRD	Median OS	Other survival outcomes	HSCT rate after salvage therapy
		d:1–5) + IDA (6 mg/m^2 d: 1–3) + G-CSF (400 μg/m^2 d:1–5)							
Bergua et al. 2016 [95]	Non-RCT, RETROSP, MC, 2-Arms	FLAG-IDA: Ara C (2 g/m^2 d:2-5) + FLU (30 mg/m^2 d:2-5) + IDA (10 mg/m^2 d:2-4) + G-CSF (300 μg/m^2 d:1-3)	221	54 (16-76) in both arms	CR: 109 (50)	14.6 m in both arms	8.4 m OS at 2 y & 5 y: 36 & 23%	mEFS 2.4 m in both arms	92 (36) HSCT, 86 allo-HSCT & 6 auto-HSCT, in both arms
		or							
		FLAGO-IDA: Ara C (2 g/m^2 d:2-5) + FLU (30 mg/m^2 d:2-5) + IDA (10 mg/m^2 d:2-4) + GO (3 mg/m^2 d:1) + G-CSF (300 μg/m^2 d:1-3)	38 In all: 61 ER, 57 LR, 135 RF		CR: 22 (61) In all, CR: 132 (51) In RF, CR: 75 (56) In ER, CR: 16 (26) In LR, CR: 38 (67) In R HSCT, CR: 72 (67) ED: 24 (9)		8.4 m OS at 2 y & 5 y: 23 & 18%		
Fludarabine + Ara-C + mitoxantrone regimens ± G-CSF: MITO-FLAG									
Luo et al. 2013 [96]	Non-RCT, RETROSP, UC, 1-Arm	MITO-FLAG: Ara-C (1 g/m^2/12 h d:1–5) + MITO (7 mg/m^2 d: 1, 3, 5) + FLU (30 mg/m^2 d: 1–5) + G-CSF (5 μg/kg d:0 until WBC > 20 × 10^9/l)* 1–2 courses	45 (25 ER, 20 LR)	34 (17–61)	CR: 23 (51) In R, CR: 29 (64) ER, CR: 16 (55) LR, CR: 13 (65) ED: 4 (9)	NA	7 m OS at 4 y: 19%	mDFS 10 DFS at 4 y: 29%	9 (20) allo-HSCT
Thiel et al. 2015 [97]	RCT, Phase III, MC, 2-Arms	MITO-FLAG (B): Ara C (1 g/m^2/12h d:1-5) + MITO (7 mg/m^2 d: 1, 3, 5) + FLU (15 mg/m^2/12h d: 1-5) + G-CSF (5 μg/kg 9 ()d:0 until WBC > 0.5x10^9/l for 3 d)	127 (40 ER, 20 LR, 67 RF, 1 ≥2ndR)	58 (26-70)	CR: 69 (54) In RF, CR: 30 (45) In R, CR: 39 (65) ER, CR: 23 (58) LR, CR: 16 (80)	NA	7.1 m OS at 2 & 5 y: 29 & 23%	mEFS 2.9 m mDFS 7.8 m	HSCT 27 (21), 26 allo-HSCT & 1 auto-HSCT
		or							
		MITO-FLAG (CI): Ara C (150 mg/m^2 CI	124 (39 ER, 21 LR, 63 RF, 1 ≥2ndR)	60 (19-70)	ED: 4 (3) CR: 53 (43)		6.6 m	mEFS 2.0 m mDFS 7.1 m	28 (23) allo-HSCT

Table 4 (continued)

Study, year	Design	Chemotherapy scheme	*N* (R/RF)	Age, median (range)	Induction outcome [n (%)]	Median CRD	Median OS	Other survival outcomes	HSCT rate after salvage therapy
		d:1-5) + MITO (7 mg/m^2 d: 2, 4, 6) + FLU (15 mg/m^2/12h d:1-6 (11 doses)) + G-CSF (5 μg/kg d:0 until WBC > 0.5x10^9/l for 3 d)			In RF, CR: 21 (33) In R, CR: 32 (53) ER, CR: 18 (46) LR, CR: 14 (67) In ≥2ndR, CR: 1 (100) ED: 7 (6)		OS at 2 & 5 y: 24 & 19%		
Fludarabine + Ara-C + daunorubicin regimens ± G-CSF									
Camera et al. 2009 [98]	Non-RCT, PROSP, MC, 1-Arm	FLAD: Ara-C (390 mg/m^2 B d:1; 1.9 g/m^2 d:1–3) + FLU (10 mg/m^2 B d:1; 25 mg/m^2 d:1–2) + DNX (60 or 80 or 100 mg/m^2 d:2–4)	61 R-RF (45 R, 16 RF)	43 (19–81)	CR: 32 (52) In RF, CR: 7 (44) In R, CR: 25 (56) ED: 7 (12)	NA	5.8 m	mDFS 7.3 m	19 (31) HSCT, 14 allo-HSCT and 5 auto-HSCT
De Astis et al. 2014 [99]	Non-RCT, RETROSP, UC, 1-Arm	FLAD: Ara-C (2 g/m^2 d:1–3) + FLU (30 mg/m^2 d:1–3) + DNX (100 mg/m^2 d:1–3) + G-CSF (300 μg d:1 until neutrophil recovery)	41 (30 R, 11 RF)	60 (18–77)	CR: 22 (53) In RF, CR: 0 (0) In R, CR: 22 (73)	NA	9 m	mDFS 9 m	10 (24) allo-HSCT
Cladribine + Ara-C + mitoxantrone regimens ± G-CSF: MITO-CLAG									
Wrzesien-Kus et al. 2005 [100]	Non-RCT, RETROSP, Phase II, MC, 1-Arm	CLAG-M: 2-CdA (5 mg/m^2 d:1–5) + Ara-C (2 g/m^2 d:1–5) + MITO (10 mg/m^2 d:1–3) + G-CSF (300 μg d:0–5)	43 (18R, 25 RF)	44 (20–66)	CR: 21 (49) ED: 2 (5)	NA	5.5 m	mDFS: 6.1 m	7 (16) HSCT, 5 allo-HSCT and 2 auto-HSCT
Wierzbowska et al. 2008 [101]	Non-RCT, RETROSP, Phase II, MC, 1-Arm	CLAG-M: 2-CdA (5 mg/m^2 d:1–5) + Ara-C (2 g/m^2 d:1–5) + MITO (10 mg/m^2 d:1–3) + G-CSF (300 μg d:0–5)	114 (39R, 75 RF)	45 (20–66)	CR: 66 (58) ED: 8 (7)	NA	9 m OS at 4 y: 14%	mDFS: 17 m DFS at 4 y: 30%	26 (23) HSCT, 20 allo-HSCT and 6 auto-HSCT
Halpern et al. 2017	Non-RCT, PROSP -RETROSP,	G-CLAM: 2-CdA (5 mg/m^2	41[b]	51 (19–69)[b]	CR: 21 (51)[b] ED: 3 (7)[b]	NA	8.1 m[b]	NA	15 (37) allo-HSCT[b]

Table 4 (continued)

Study, year	Design	Chemotherapy scheme	*N* (R/RF)	Age, median (range)	Induction outcome [n (%)]	Median CRD	Median OS	Other survival outcomes	HSCT rate after salvage therapy
[90]	Phase I/II, MC, 2-Arms (see above and in Table 5)	d:1–5) + Ara-C (2 g/m^2 d:1–5) + MITO (10 mg/m^2 d:1–3) + G-CSF (300 or 480 μg d:0–5) RETROSP. COHORT	(24 R, 17 RF)						
Fludarabine + Ara-C + other agent regimens ± G-CSF									
Martin et al. 2009 [92]	Non-RCT, RETROSP, UC, 2-Arms (see above in this table)	FLAG-IM: Ara-C (2 g/m^2 d:1–5) + FLU (25 mg/m^2 d:1–5) + IDA (12 mg/m^2 d:1–3) + GO (9 mg/m^2 d:8) ± G-CSF (37 patients)	48 (30 R, 8 RF, 10 ≥ 2ndR)	47 (20–68)	CR: 27 (56) ED: 11 (23)	8.3 m	5.0 m	mDFS 4.1 m	11 (23) allo-HSCT
Jabbour et al. 2012 [85]	Non-RCT, PROSP, Phase II, MC, 2-Arms (see above in this table)	Ara-C (0,5 g/m^2/12 h d:1–5) + FLU (15 mg/m^2/12 h d:1–5) + GO (3 mg/m^2 d:1) *1–2 courses If age ≥ 65 y, d:1–4; if PS = 3, d:1–3	59[a] (R-RF)	62 (19–85)[a]	CR: 18 (30)[a]	NA	7.4 m[a] OS at 2 y: 38%[a]	mDFS 1.2 m[a]	NA
Clofarabine + Ara-C regimens ± G-CSF									
Becker et al. 2011 [87]	Non-RCT, PROSP, Phase I/II, MC, 1-Arm	CLOFA (15 or 20 or 25 mg/m^2 d:1–5) + Ara-C (2 g/m^2 d:1–5) + G-CSF (5 μg/kg d:0 until neutrophils > 2 × 10^9/l for 2 d)	46 (15 R, 18 RF, 13 ≥ 2ndR)	53 (19–69)	CR: 28 (61) In RF, CR: 12 (67) In R, CR: 9 (60) ER, CR: 6 (26) LR, CR: 3 (60) In ≥2ndR, CR: 5 (39)	NA	9 m	NA	25 (54) allo-HSCT
Faderl et al. 2012 [21]	RCT, Phase III, MC, doble-blinded, 2-Arms (see Table 1)	CLOFA (40 mg/m^2 d1–5) + Ara-C (1 g/m^2 d:1–5)	162 (74 R, 88 RF)	67 (55–82)	CR: 76 (47) ED 30d: 25 (16)	7.6 m	6.6 m	EFS at 14 m: 38%	34 (21) HSCT
Scappini et al. 2012 [102]	Non-RCT, PROSP, MC, 1-Arm	CLOFA (22.5 mg/m^2 d1–5) + Ara-C (1 g/m^2 d:1–5)	47 (13 R, 20 RF, 14 ≥ 2ndR)	50.5 (21–71)	CR: 24 (51) ED: 6 (13)	7.9 m	6.6 m	NA	13 (28) allo-HSCT
Roberts et al. 2015 [103]	Non-RCT, PROSP, MC, 2-Arms (see Table 6)	CLOFA (40 mg/m^2 d:2–6) + Ara-C	65[c] (47R, 18 RF)	49 (22–70)[c]	CR: 12 (19)[c]	NA	3 m in both arms	NA	12 (14) allo-HSCT in both arms

Table 4 (continued)

Study, year	Design	Chemotherapy scheme	*N* (R/RF)	Age, median (range)	Induction outcome [n (%)]	Median CRD	Median OS	Other survival outcomes	HSCT rate after salvage therapy
		(1 g/m^2 d:1–5)							

OS and CR has been estimated in months in the cases that it was reported in days (1 month = 30 days) and weeks (1 month = 4.3 weeks). References [41, 104–123] are not showed in Table 4 because the total number of R/R AML patients were less than 40. The full version of Table 4 is included in the Supplemental Material as Supplemental Table 4

≥2nd R second or beyond relapse, *2-CdA* cladribine, *6-MP* 6-mercaptopurine, *6-TG* 6-thioguanine, *AML* acute myeloid leukemia, *Ara-C* cytarabine, *B* bolus, *CI* continuous infusion, *CLOFA* clofarabine, *CML-BP* chronic myeloid leukemia in myeloid blast phase, *CR* complete remission, *d* days, *DNR* daunorubicin, *DNX* liposomal daunorubicin, *ED* early death, *EFS* event-free survival, *ETOP* etoposide, *FLU* fludarabine, *G-CSF* granulocyte colony-stimulating factor, *m* months, *HSCT* hematopoietic stem cell transplantation, *IDA* idarubicin, *mD* median duration, *mDFS* median disease-free survival, *MDS* myelodysplastic syndrome, *MITO* mitoxantrone, *mOS* median overall survival, *N* population of relapsed/refractory patients with AML, *NA* not available, *NR* not reached, *OS* overall survival, *R* relapse, *RCT* randomized clinical trial, *RF* refractory, *RFS* relapse-free survival, *SEC* AML secondary, *TOPO* topotecan, *UT* untreated, *w* weeks, *y* year

[a] Results of the entire cohort, including 93 R-RF AML, 5 high-risk MDS, and 9 CML-BP. The CR rate was calculated in the different arms (Ara-C + FLU ± GO), whereas OS and DFS in the entire cohort

[b] Results of the entire cohort, including 31 AML, 10 MDS

[c] Results in the entire cohort, including 49 AML de novo, 15 secondary, and 1 MDS patients with R-RF

should mention that the first study using a high dose of Ara-C (HiDAC) of 3 g/m^2/12 h was performed in a small cohort of younger R/R patients showing a higher CR rate of 47%, but the mCRD was 5 months [15].

In general, the HiDAC schedules showed higher wmCR rate of 28% (range 12–47%) [8, 15, 16, 18, 19, 23] than intermediate doses of Ara-C (IDAC), 1 g/m^2/12 h or 500 mg/m^2/12 h, with mCR rate of 20.6% (range 19–25%) [8, 17, 20–22]. However, Estey et al. did not obtain differences between HiDAC and IDAC cohorts in a retrospective non-RCT (CR 23 and 25%) [8]. A study analyzed the use of Ara-C continuous infusion (CI) in a small relapsed cohort obtaining poor results (CR 12%) [24].

Anthracycline plus cytarabine-based regimens

Thirty-eight studies based on these regimens were included (Table 2) [4, 5, 7, 15, 19–22, 25–57]. The most studied combination was mitoxantrone plus Ara-C (17 studies) [4, 5, 19, 25–29, 39–41, 43, 46, 47, 50–52]. This scheme showed a wmCR rate of 50% (range: 32–79%), wmCRD of 4.8 months (range 2.9–12), and wmOS of 5.4 months (range 3–12). Other anthracyclines were used in combinations with Ara-C:

- Daunorubicin (two studies), with CR rates from 33 to 59% [15, 30].
- Amsacrine (seven studies), with a wmCR rate of 54.3% (range 46–75%) [7, 27, 42, 44, 48, 49, 53].
- Idarubicin (four studies), with CR rates from 35 to 60% [31, 32, 45, 55].
- Aclarubicin (four studies), always plus granulocyte colony-stimulated factor (G-CSF), with CR rates from 51 to 83% [33, 34, 54, 57].
- Liposomal daunorubicin (three studies), with CR rates from 7 to 47% [35, 36, 56].
- Liposome-encapsulated fixed-molar-ratio formulation of Ara-C plus daunorubicin (one study), with CR rate of 37% [37].

The published evidence did not report superiority of any of the anthracyclines, although the experience with mitoxantrone is more extensive. A RCT compared two schedules combining HiDAC with two different anthracyclines, mitoxantrone and amsacrine [27]. Both regimens showed similar CR rates (58 vs. 46%) and mOS (12 vs. 8 months), but severe gastrointestinal toxicity was significantly higher with amsacrine (27 vs. 4%, $p = 0.021$). A retrospective study from the French AML Intergroup performed in a subgroup of core-binding factor (CBF) AML in first relapse showed the highest CR rate of 88% with combinations of Ara-C and different anthracyclines [38].

Table 5 Studies of salvage therapy with monotherapies or other intensive combinations in relapse or refractory AML patients

Study, year	Design	Chemotherapy scheme	*N* (R/RF)	Age, median (range)	Induction outcome [*n* (%)]	Median CRD	Median OS	Other survival outcomes	HSCT rate after salvage therapy
Monotherapies									
Bennett et al. 1984 [124]	Non-RCT, PROSP, Phase II, MC, 1-Arm	ETOP (100 mg/m^2 d:1–5 every 3 w until relapse). Retreatment with 125 mg/m^2 if CR-PR is NR	38 (28R, 10RF)	NA	CR: 2 (5) In RF, CR: 1 (10) In R, CR: 1 (4)	16 m	In CR, 9 m No CR, 2.8 m	NA	NA
Paciucci et al. 1984 [39]	Non-RCT, UC, 2-Arms (see Table 2)	MITO (1) (8–14 mg/m^2 d:1–5)	12 (12 R or RF)	37 (5–73)[a]	CR: 1 (8) ED: 2 (17)	NA	NA	NA	NA
Vogler et al. 1986 [23]	RCT, Phase III, MC, 2-Arms (see Supplemental Table 1)	AMSA (75 mg/m^2 d:1–7)	23 (13 R, 6 RF, 4 ≥ 2ndR)	57 (20–74)	CR: 3 (13) ED: 4 (17)	2.8 m	NA	NA	NA
Harousseau et al. 1987 [125]	Non-RCT, PROSP, Phase II, MC, 1-Arm	IDA (7 mg/m^2 d:1-5) or	19 (12 R, 7 RF-≥2ndR)	50 (21-77)[b]	CR: 3 (16) In R, CR: 2 (17) In RF-≥2ndR, CR: 1 (14)	NA	NA	NA	NA
		IDA (8 mg/m^2 d:1-5)	23 (16 R, 7 RF-≥2ndR)	56 (18-74)[b]	CR: 6 (26) In R, CR: 5 (31) In RF-≥2ndR, CR: 1 (14)				
Bezwoda et al. 1990 [126]	Non-RCT, PROSP, Phase II, MC, 1-Arm	MITO (12 mg/m^2 d:1–5)	62 (45 R, 17 RF)	NA	CR: 27 (44) In RF, CR: 4 (24) In R, CR: 23 (51) ED: 2 (3)	1.6 m[c]	4 m[c]	NA	None
Goldberg et al. 1993 [127]	Non-RCT, PROSP, UC, 2-Arms (see below in this table)	MITO (12 mg/m^2 d:1–5)	50[d] (50 R or RF)	Mean 47 y in both arms[d]	CR: 14 (28)[d] ED: 13 (46)[d]	NA	NA	NA	NA
Vogler et al. 1992 [128]	Non-RCT, PROSP, Phase II, MC, 1-Arm	CARBO (315 mg/m^2 CI d: 1–5). 2 courses if blasts in bone marrow biopsy d 14	36 (14 R, 7 ≥ 2ndR, 15 RF)	49 (21–80)	CR: 6 (17) In RF, CR: 1 (7) In R, CR: 5 (36)	1.5 m	NA	NA	3 (8) HSCT
Welbom et al. 1995 [129]	Non-RCT, PROSP, Phase II, MC, 1-Arm	CARBO (300 mg/m^2 CI d: 1–5)	45 (37 R, 8 RF)	48 (23–71)	CR: 3 (7) In RF, CR: 0 (0) In R, CR: 3 (8) ED: 12 (27)	4 m	2 m	NA	NA
Kornblau et al. 1996 [104]	Non-RCT, PROSP, Phase I/II, UC, 2-Arms (see Table 4)	2-CdA (5 to 13 mg/m^2 d:1–7)	27 (21 R, 3 RF, 3 ≥ 2ndR)	56 (19–80)	CR: 0 (0) ED: 2 (7)	NA	2.4 m	NA	NA
Gordon et al. 2000 [130]	Non-RCT, PROSP, Phase II, MC, 1-Arm	2-CdA (17 mg/m^2 d:1–5)	15 (9 R, 6 RF)	60 (29–75)	CR: 0 (0)	8.1 m	1.9 m	NA	NA
				62 (22-89)	CR: 39 (23)	5.1 m	3.5 m	NA	20 (11) HSCT

Table 5 (continued)

Study, year	Design	Chemotherapy scheme	*N* (R/RF)	Age, median (range)	Induction outcome [*n* (%)]	Median CRD	Median OS	Other survival outcomes	HSCT rate after salvage therapy
Roboz et al. 2014 [131]	RCT, Phase III, MC, 2-Arms	ELACYT (2 g/m^2 d:1-5 every 3 w)	191 (119 R, 72 RF)		ED 30d: 31 (17) ED 60d: 63 (34) CR: 35 (21)				
		or Control treatment: HiDAC (Ara C 1-6 g/m^2 d:1-6), MEC, FLAG/FLA-Ida, low-dose Ara C, AZA or DAC, hydroxyurea, supportive care	190 (122 R, 68 RF)	63 (19-83)	ED 30d: 27 (15) ED 60d: 54 (30)	3.7 m	3.3 m		21 (11) HSCT
Knapper et al. 2014 [132]	Non-RCT, PROSP, MC, 1-Arm	ELACYT (2 g/m^2 d:1–5 every 3 w)	36 (30 R, 9 RF, 4 ≥2ndR)[e]	63 (18–77)	CR: 16 (44)	NA	4.7 m OS at 6 m: 40%	NA	4 (9) allo-HSCT
Ara-C + other agents									
Capizzi et al. 1988 [16]	RCT, Phase III, MC, 2-Arms (see Table 1)	Ara-C (3 g/m^2/12 h d:1–2; 8–9; 15-16[a]) + ASNase (6000 IU/m^2 d:2)	95 (69 R, 24 RF)	52 (NA), in both arms	CR: 36 (38) In RF, CR: 10 (42) In R, CR: 26 (39) ED: 29 (31)	4.9 m In RF, 9 m	In < 60 y, 7.9 m	NA	HSCT excluded
Vogler et al. 1994 [18]	RCT, Phase III, MC, 2-Arms (see Table 1)	Ara-C (3 g/m^2/12 h d:1–6) + ETOP (100 mg/m^2 d:7–9)	66 (24 ER, 20 LR, 17RF)	NA	CR: 25 (38) In RF, CR: 4 (27) In R, CR: 20 (45) ER, CR: 7 (29) LR, CR: 13 (65)	25 m	5.2 m	DFS at 5y: 8%	NA
Bergmann et al. 1995 [133]	Non-RCT, PROSP, Phase II, MC, 1-Arm	Ara-C (600 mg/m^2/12 h d:1–4) + ETOP (100 mg/m^2 d:1–5)	66 (66 R)	55 (13–67)	CR: 37 (56)	NA	NA	NA	6 (9) HSCT, 4 auto-HSCT and 2 allo-HSCT
Giles et al. 2009 [20]	RCT, Phase III, MC, doble-blinded, 2-Arms (see Table 1)	Ara-C (1.5 g/m^2 d:1–3) + Laromustine (600 mg/m^2 d:2)	177 (177 R)	59 (22–82)	CR: 62 (35) ED: 19 (11)	NA	4.2 m	mPFS 1.8 m	19 (11) allo-HSCT
Litzow et al. 2010 [36]	RCT, Phase II, MC, 2-Arms (see table 2)	Ara C (1 g/m^2 d:1-4) + GO (6 mg/m^2 d:5)	26 (16 R, 10 RF)	60 (27-75)	CR: 3 (12)	NA	3.7 m	NA	NA
		or Ara C (1 g/m^2 d:2-6) + CY (300 mg/m^2/12h d:1-3) + TOPO (1.5 mg/m^2 d:2-6)	27 (18 R, 9 RF)	53 (25-78)	CR: 1 (4)		3.8 m		
Hospital et al. 2014 [38]	Non-RCT, RETROSP, MC, 2-Arms (see Tables 2 and 3)	GO (6 to 9 mg/m^2 d:1 or 3 mg/m^2 d:1, 4, 7) + Ara-C ± anthracycline	48 CBF-AML at R	46 (20–76)	CR: 42 (88)	NA	OS at 5 y: 65%	DFS at 5 y: 68%	31 (65) HSCT, 28 allo-HSCT and 3 auto-HSCT

Table 5 (continued)

Study, year	Design	Chemotherapy scheme	*N* (R/RF)	Age, median (range)	Induction outcome [*n* (%)]	Median CRD	Median OS	Other survival outcomes	HSCT rate after salvage therapy
Ravandi et al. 2015 [22]	RCT, Phase III, MC, doble-blinded, 2-Arms (see Table 1)	VOSAROXIN (90 mg/m^2 d:1–4 first cycle; 70 mg/m^2 d:1–4) + Ara-C (1 g/m^2 d:1–5)	356 (127 ER, 77 LR, 152 RF)	64 (20–80)	CR: 132 (37) In RF, CR: 42 (28) In R, CR: 80 (39) ER, CR: 34 (35) LR, CR: 46 (60) ED 30d: 28 (8) ED 60d: 70 (20)	NA	7.5 m	NA	107 (30) allo-HSCT
Halpern et al. 2017 [90]	Non-RCT, PROSP -RETROSP, Phase I/II, MC, 2-Arms (see Table 4)	DAC (20 mg/m^2 d:1–5 or 1–7 or 1–10) 5 d break + Ara-C (1 g/m^2 d:1–5) + MITO (8 mg/m^2 d:1–5) + ETOP (100 mg/m^2 d:1–5)	51 (32 R, 19 RF)	55 (19–75)[f]	CR: 16 (31)[f] ED: 8 (15)[f]	NA	4.9 m[f]	NA	13 (25) allo-HSCT[f]
Anthracyclines + other agents									
Ho et al. 1988 [134]	Non-RCT, PROSP, Phase II, MC, 1-Arm	MITO (10 mg/m^2 d:1–5) + ETOP (100 mg/m^2 d:1–5)	52 (20 R, 21 RF, 11 ≥ 2ndR)	47 (19–71)[g]	CR: 20 (39) ED: 2 (3)	4.7 m[g], excluding HSCT	8 m[g]	NA	4 (9) HSCT auto-HSCT[g]
Rowe et al. 1990 [135]	Non-RCT, PROSP, Phase II, MC, 1-Arm	MITO (12 mg/m^2 d:1–5) + ETOP (100 mg/m^2 d:1–5)	44 ANLL (24 R, 14 RF, 6 ≥ 2ndR)	46 (18–63)	CR: 20 (45) In RF, CR: 3 (14) In R, CR: 15 (63) In ≥2ndR, CR: 6 (50) ED: 6 (14)	3.5 m	3 m	NA	NA
Hilbe et al. 1994 [136]	Non-RCT, RETROSP, UC, 1-Arm	ACLA (60 mg/m^2 d:1–5) + ETOP (100 mg/m^2 d:1–5)	10 (4 R,6 RF)	49 (20–69)	CR: 4 (40) ED: 3 (30)	7.5 m	NA	NA	NA
Kern et al. 1998 [137]	Non-RCT, PROSP, Phase II, MC, 1-Arm	ACLA (60 mg/m^2 d:1–5) + ETOP (100 mg/m^2 d:1–5)*1–2 courses	37 (37 ≥ 2ndR)	42 (18–81)	CR: 9 (24) ED: 8 (22)	0.8 m	3.2 m	mDFS 3.2 m	4 (11) HSCT
Boyiadzis et al. 2011 [138]	Non-RCT, PROSP, UC, 1-Arm	MITO (10 mg/m^2 d:1–3) + ETOP (100 mg/m^2 d: 1–5) + GO (3 mg/m^2 d:6)	5 R-RF	57 (33–61)	CR: 3 (60)	NA	NA	NA	1 (20) HSCT allo-HSCT
Van Den Neste et al. 1998 [139]	Non-RCT, PROSP, Phase II, MC, 1-Arm	DNR (50 mg/m^2 d:5–7) + 2-CdA (0.1 mg/kg d:1–7) in 14 pts 2-CdA monotherapy in 5 pts	19 (12 R, 7 RF)	57 (18–66)	CR: 0 (0)	Not applicable	1.9 m	NA	NA
Faderl et al. 2008 [105]	Non-RCT, PROSP, Phase II, UC, dose-finding, 2-Arms (see Table 4)	IDA (8 or 10 or 12 mg/m^2 d:1–3) + CLOFA (15 or 22.5 or 30 mg/m^2 d: 1–5)	23 (14 R, 9 RF)	58 (24–71)	CR: 3 (13)	4.4 m	NA	NA	NA
Apostolidou et al. 2003 [140]	Non-RCT, PROSP, UC, 1-Arm	MITO (12 mg/m^2 d:1–3) + GEMCIT (10 mg/m^2/min for a 12 h period)	18 (12 R, 6 RF)	54 (18–80)	CR: 2 (11) ED: 3 (17)	3 m	NA	NA	NA
Goldberg et al. 1993 [127]	Non-RCT, PROSP, UC, 2-Arms (see above in this table)	MITO (12 mg/m^2 d:1–5) + AZA (200 mg/m^2	53[d] (53 R or RF)	Mean 47 y in both arms[d]	CR: 8 (15)[d] ED: 9 (17)[d]	NA	NA	NA	NA

Table 5 (continued)

Study, year	Design	Chemotherapy scheme	*N* (R/RF)	Age, median (range)	Induction outcome [*n* (%)]	Median CRD	Median OS	Other survival outcomes	HSCT rate after salvage therapy
		d:7–9); if > 20% abnormal cells in bone marrow day 6 biopsy							
Willemze et al. 1997 [141]	RCT, Phase II, MC, 2-Arms	DAC (125 mg/m^2/12h d:1-6) + AMSA (120 mg/m^2 d:6-7)	30 R-RF AL (22 R, 5 ≥2ndR)	53 (17-67)	CR: 8 (27)	NA	NA	mDFS 8 m DFS at 1 y: 20% in the entire cohort	NA
		or DAC (125 mg/m^2/12h d:1-6) + IDA (12 mg/m^2 d:5-7)	33 R-RF AL (27 R, 3 ≥2ndR) 57 AML in both arms (27 & 30 pts)	57 (21-76)	CR: 15 (45) In AML (2-arms), CR: 22 (39) In R, CR: 18 (37) In ≥2ndR, CR: 4 (50)				
Carboplatin + other agents									
Sanz et al. 1992 [142]	Non-RCT, RETROSP, Phase II, UC, 1-Arm	CARBO (300 mg/m^2 CI d: 1–5) + ETOP (100 mg/m^2 d: 1–3 or 1–4)	20 ANLL[h]	43 (20–67)[h]	CR: 8 (40) ED: 5 (25)[h]	NA	NA	NA	NA
Letendre et al. 1995 [143]	Non-RCT, RETROSP, UC, 1-Arm	CARBO (200 mg/m^2 CI d: 1–5) + ETOP (125 mg/m^2 CI d: 1–5)	7 ANLL (3 R, 3 RF, 1 ≥ 2ndR)	52 (16–74)	CR: 0 (0)	Not applicable	NA	NA	NA
Amadori et al. 1996 [144]	Non-RCT, RETROSP, Phase II, UC, 1-Arm	Ara-C (500 mg/m^2 d:1–3, 8–10) + ETOP (100 mg/m^2 d:1–3, 8–10) + CARBO (150 mg/m^2 CI d:1–3, 8–10)	18 (5 R, 6 RF, 7 ≥ 2ndR)	33 (2–50)[i]	CR: 9 (50) In RF, CR: 2 (33) In R, CR: 1 (20) In ≥2ndR, CR: 6 (86)	NA	7 m[i]	mDFS 4 m[i]	6 (19) HSCT, 2 allo-HSCT and r auto-HSCT[i]
Kornblau et al. 1998 [145]	Non-RCT, RETROSP, UC, 1-Arm	Ara-C (1 g/m^2 d:1–3) + CY (1 g/m^2 d: 1–3) + CARBO (150 mg/m^2 d: 1–3) + ETOP (200 mg/m^2 d: 1–3)	25 (22 R, 3 RF)	54 (24–79)	CR: 3 (12) ED: 6 (24)	NA	NA	NA	2 (8) allo-HSCT
Belhabri et al. 1999 [146]	RCT, Phase II, MC, 2-Arms	IDA (12 mg/m^2 d:1-3) + CARBO (200 mg/m^2 CI d: 3-7)	25 (9 R, 7 RF, 9 ≥2ndR)	65 (20-74)[j]	CR: 8 (29) In RF, CR: 1 (14) In R, CR: 4 (44) In ≥2ndR, CR: 3 (33)	NA	2 m[j]	mDFS 2 m[j]	1 (2) allo-HSCT in both arms[j]
		or MITO (12 mg/m^2 d:1-3) + CARBO (200 mg/m^2 CI d: 3-7)	23 (10 R, 7 RF, 6 ≥2ndR)	66 (19-78)[j]	ED: 5 (18) CR: 7 (28) In RF, CR: 1 (14) In R, CR: 3 (30) In ≥2ndR, CR: 1 (17) ED: 7 (28)	NA	2.5 m[j]	mDFS 2.5 m[j]	
Ferrá et al. 2000 [147]	Non-RCT, RETROSP, UC, 1-Arm	MECA: MITO (8 mg/m^2 CI d:1–5) + ETOP (100 mg/m^2 d: 1–3) + CARBO (200 mg/m^2 CI d: 7–8) + Ara-C (500 mg/m^2/12 h d:7–8) *1–2 courses	31 (26 R, 20 RF, 5 ≥ 2ndR)[k]	34 (36–64)[k]	CR: 10 (32)	10.4 m[k]	8.5 m	mDFS 4.3 m	10 (32) HSCT

OS and CR has been estimated in months in the cases that it was reported in days (1 month = 30 days) and weeks (1 month = 4.3 weeks). References [148–153] are not showed of Table 5 because the total number of R/R AML patients were less than 40. The full version of Table 5 is included in the Supplemental Material as Supplemental Table 5

≥2nd R second or beyond relapse, *2-CdA* cladribine, *6-MP* 6-mercaptopurine, *6-TG* 6-thioguanine, *ACLA* aclarubicin, *ALL* acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *AMSA* amsacrine, *ANLL* acute nonlymphocytic leukemia, *Ara-C* cytarabine, *ASNase* asparraginase, *AZA* azacitidine, *B* bolus, *CARBO* carboplatin, *CBF-AML* core-binding factor-acute myeloid leukemia, *CI* continuous infusion, *CLOFA* clofarabine, *CML-BP* chronic myeloid leukemia in myeloid blast phase, *CR* complete remission, *d* days, *CY* cyclophosphamide, *DAC* decitabine, *DNR* daunorubicin, *DNX* liposomal daunorubicin, *DOX* doxorubicin, *ED* early death, *EFS* event-free survival, *ELACYT* elacytarabine, *ETOP* etoposide, *GEMCIT* gemcitabine, *GO* gemtuzumab ozogamicin, *HSCT* hematopoietic stem cell transplantation, *IDA* idarubicin, *m* months, *mD* median duration, *mDFS* median disease-free survival, *MDS* myelodysplastic syndrome, *MITO* mitoxantrone, *mOS* median overall survival, *mPFS* median progression-free survival, *N* population of relapsed/refractory patients with AML, *NA* not available, *NR* not reached, *OS* overall survival, *R* relapse, *RCT* randomized clinical trial, *RF* refractory, *RFS* relapse-free survival, *SEC* AML secondary, *TOPO* topotecn, *UT* untreated, *w* weeks, *y* year

[a] Results of all cohort of 47 AL. The cohort treated with MITO monotherapy included 12 AML R-RF, 12 ALL, 2 CML-BP patients

[b] Results of the entire, including 42 AML (28 R, 14 RF), 8 secondary, and 5 CML-BP patients

[c] Results of the entire cohort of AL R or RF patients, including ANLL (62 AML R-RF, 3 CML) and 15 ALL patients

[d] Results of the entire cohort of 106 ALNLL or CML-BP patients (54 R, 60 RF). CR rates mixed the results in ALNLL and CML-BP patients (MIT arm included 50 patients, and the MIT + AZA arm 53 patients)

[e] Distribution of R-RF patients of the 43 initial cohort, including 36 evaluable and 7 non-evaluable patients

[f] Results of the entire cohort, including 45 AML, 6 MDS

[g] Results of the entire cohort, including 20 R, 21 RF, 11 ≥2nd R, 9 SEC

[h] Results of the entire cohort of high risk ANLL patients, including 15 ANLL (3 R, 8 RF, 4 secondary to MDS) and 5 CML-BP patients

[i] Results of the entire cohort, including 18 AML and 13 CML-BP

[j] Results of the entire AML cohort, including 25 R-RF AML and 3 UT AML in the IDA + CARBO arm, and 23 R-RF AML and 2 UT AML in the MITO + CARBO arm

[k] Results of the entire cohort of 51 AL R or RF patients, including 31 AML and 19 ALL patients, and 1 biphenotypic leukemia

Anthracycline plus cytarabine plus third-agent based regimens

The addition of a third neoplastic agent, usually etoposide, to the Ara-C plus anthracycline combination has been broadly used (Table 3) [34, 38, 58–72, 74–82]. The combination of mitoxantrone, etoposide, and Ara-C (MEC or EMA schemes) is the most reported with a wmCR rate of 52.5% (range 24–68%), wmCRD of 5.3 months (range 1.5–12), and wmOS of 6.8 months (range 2.1–10.1) [58–67, 79–82]. The addition of G-CSF did not modify the efficacy of MEC scheme in one non-RCT and two RCTs [59, 60, 63]. Similar schemes with other anthracyclines plus etoposide and Ara-C have been tested, including idarubicin (one study) [68], daunorubicin (two studies) [69, 70], amsacrine (one study) [71], and aclarubicin (one study) [34], with CR rates from 33 to 71%.

The MIDAM combination of mitoxantrone, Ara-C, and gemtuzumab ozogamicin (GO) was analyzed in five different retrospective studies, with a wmCR rate of 59.4% (range 53–88) and wmOS of 12.6 months (range 7.2–16) [38, 75–78]. In this analysis, we excluded the study of Hospital MA et al. performed only in R/R CBF-AML, obtaining a 88% CR rate and an OS at 5 years of 65% (65% of patients received HSCT) [38]. The most recent study compared the use of GO as a single dose or fractionated in three doses, showing a non-significant better results with fractionated scheme [77]. A new scheme combining HiDAC, mitoxantrone, GO and all-trans retinoic acid (ATRA) in AML refractory to first induction reported CR rate of 51% and mOS of 16 months [78].

Other schemes were tested in a single study, combining Ara-C plus anthracyclines with vincristine [73], dacarbazine [74], or decitabine [72].

Purine analogue plus cytarabine-based regimens

Purine nucleoside analogs have shown a synergistic interaction with Ara-C through increasing the Ara-C intracellular accumulation, [8, 104, 106], and the addition of G-CSF has been related to higher Ara-C-mediated cytotoxicity [168]. Our search obtained 48 studies combining purine analogs with Ara-C-based schedules (Table 4) [8, 21, 32, 41, 67, 70, 83–123, 169].

– Fludarabine + Ara-C regimens

Thirteen studies included combinations of fludarabine and Ara-C with or without G-CSF, schemes usually called FLA and FLAG, respectively [8, 70, 83–86, 88, 106–110, 123], showing a wmCR rate of 45.3% (range 19–63%), wmCRD of 9.8 months (range 2.3–17.1), and wmOS of 7.2 months (range 3.2–14.3). Despite the differences observed between wmCR rates of FLA (28.8%, range 19–39%) [8, 70, 85, 86, 123] and FLAG (53.3%, range 20–63%) [70, 83, 84, 86, 88,

Table 6 Studies of salvage therapy with non-intensive approaches in relapse or refractory AML patients

Study, year	Design	Chemotherapy scheme	*N* (R/RF)	Age, median (range)	Induction outcome [n (%)]	Median CRD	Median OS	Other survival outcomes	HSCT rate after salvage therapy
Ara-C non-intensive regimens									
Jensen et al. 1994 [154]	Non-RCT, PROSP, UC, 1-Arm	Ara-C (10 mg/m^2/12 h SC d:1–21)	25 (12R, 13 RF)	45 (15–61)	CR: 11 (44) In R, CR: 6 (50) In RF, CR: 5 (38) ED: 3 (12)	NA	8 m	NA	2 (8) allo-HSCT
Venditti et al. 1995 [155]	Non-RCT, PROSP, UC, 1-Arm	Ara-C (20 mg/12 h SC d:1–10 every 4w) + ATRA (45 mg/m^2 oral)	33 (6R, 15RF)	67 (39–82)	CR: 16 (49) ED: 3 (9)	8 m	NA	NA	NA
Gemtuzumab ozogamicin monotherapy									
Lang et al. 2002 [40]	Non-RCT, PROSP, MC, 2-Arms (see Table 2)	GO (9 mg/m^2 d:1, 19, 37)	104 (104 R)	60 (22–84)	NA	NA	OS at 1.5 m: 89%	NA	NA
Larson et al. 2005 [156]	Non-RCT, PROSP, Phase II, MC, 1-Arm	GO (9 mg/m^2 d:1)*2 courses at 14 d	277 (161 ER, 116 LR)	61 (20–87)	CR: 71 (26) ER: 31 (19) LR: 40 (34) ED: 4 (0.01)	5.2 m	4.9 m	NA	25 (9), 14 allo-HSCT and 11 auto-HSCT
Taksin et al. 2007 [157]	Non-RCT, PROSP, Phase II, MC, 1-Arm	GO (3 mg/m^2 d:1, 4, 7)	57 (57 R)	64 (22–80)	CR: 19 (33) ED: 4 (7)	11 m	8.4 m	NA	7 (12) HSCT, 3 allo-HSCT and 4 auto-HSCT
Clofarabine monotherapy									
Roberts et al. 2015 [103]	Non-RCT, PROSP, MC, 2-Arms (see Table 4)	CLOFA (15–30 mg/m^2 d:1–5)	19[a] (7R, 12 RF)	72 (34–77)[a]	CR: 2 (11)[a]	NA	3 m in both arms	NA	12 (14) allo-HSCT
Azacitidine monotherapy									
Ivanoff et al. 2013 [158]	Non-RCT, RETROSP, MC, 1-Arm	AZA (75 mg/m^2 SC d:1–7 every 28 d)	47 (20 R, 27RF)	63 (29–79)	CR: 10 (21)	6 m	9 m	NA	6 (13) allo-HSCT
Itzykson et al. 2015 [159]	Non-RCT, RETROSP, MC, 1-Arm	AZA (75 mg/m^2 SC d:1–7 every 28 d)* 4 or more cycles	130 (67 R, 63 RF)	67 (50–80)	CR: 22 (17) In R, CR: 13 (19) In RF, CR: 9 (14)	11.9 m (3–40)	8.4 m OS at 1 y: 29%	NA	6 (5) allo-HSCT
Stahl et al. 2016 [160]	Non-RCT, RETROSP, MC, 2-Arms (see below in this table)	AZA (75 mg/m^2 SC d:1–7 every 28 d) or different regimens	360 All 656 (365 R, 296 RF)	NA	CR: 105 (16) in both arms	NA	6.7 m All, 6.5 m	NA	NA
Decitabine monotherapy									
	Non-RCT, RETROSP, UC, 2-Arms (see below in this table)	DAC (20 mg/m^2 d:1-10)	57 (57 R or RF)	66 (21-88) in both arms	CR: 16 (16) in both arms	NA	7 m All, 5.9 m	NA	1 (1) allo-HSCT in both cohorts

Table 6 (continued)

Study, year	Design	Chemotherapy scheme	*N* (R/RF)	Age, median (range)	Induction outcome [n (%)]	Median CRD	Median OS	Other survival outcomes	HSCT rate after salvage therapy
Ritchie et al. 2013 [161]									
Stahl et al. 2016 [160]	Non-RCT, RETROSP, MC, 2-Arms (see above in this table)	DAC (20 mg/m^2 d:1-5) or different regimens	274 All 656 (365 R, 296 RF)	NA	CR: 105 (16) in both arms	NA	5.7 m All, 6.5 m	NA	NA
Azacitidine combinations									
Raffoux et al. 2010 [162]	Non-RCT, PROSP, MC, 1-Arm	AZA (75 mg/m^2 SC d:1–7) + VPA (35 to 50 mg/kg d:1–7) + ATRA (45 mg/m^2 oral d:8–28) + 2–6 courses every 4 w	13 (13 R or RF)	72 (50–87)[b]	CR: 2 (15)	NA	2.9 m	NA	NA
Decitabine + gemtuzumab ozogamicin regimens									
Ritchie et al. 2013 [161]	Non-RCT, RETROSP, UC, 2-Arms (see above in this table)	DAC (20 mg/m^2 d:1-5) + GO (3 mg/m^2 d:5)	45 (45 R or RF)	66 (21-88) in both arms	CR: 16 (16) in both arms	NA	3.6 m All, 5.9 m	NA	1 (1) allo-HSCT in both cohorts
Daver et al. 2017 [163]	Non-RCT, PROSP, Phase II, UC, 1-Arm	DAC (20 mg/m^2 d:1–5) + GO (3 mg/m^2 d:5). If d-14 bone marrow biopsy showed ≥ 20% cellularity with ≥ 5% blast: additional DAC cycle. Post-induction: cycles every 4–8 w	33 (28 ER-RF, 5 LR-RF)	70 (27–89)[c]	CR: 8 (24) ER-RF, CR: 5 (18) LR-RF, CR: 3 (60) ED: 3 (3)	5.8 m[c] 1 m 3 m	3.5 m 8 m	NA	NA

OS and CR has been estimated in months in the cases that it was reported in days (1 month = 30 days) and weeks (1 month = 4.3 weeks). References [164–167] are not showed of Table 6 because the total number of R/R AML patients were less than 40. The full version of Table 6 is included in the Supplemental Material as Supplemental Table 6

AD aplastic death, *AML* acute myeloid leukemia, *Ara-C* cytarabine, *ATRA* all-trans retinoic acid, *AZA* azacitidine, *CLOFA* clofarabine, *CR* complete remission, *d* days, *DAC* decitabine, *DLI* donor lymphocyte infusion, *ED* early death, *GO* gemtuzumab ozogamicin, *m* months, *mCRD* median CR duration, *mDFS* median disease-free survival, *MDS* myelodysplastic syndrome, *mOS* median overall survival, *MPS* myeloproliferative syndrome, *N* population of relapsed/refractory patients with AML, *NA* not available, *NR* not reached, *OS* overall survival, *R* relapse, *RCT* randomized clinical trial, *RF* refractory, *RFS* relapse-free survival, *VPA* valproic acid, *w* weeks, *y* year

[a] Results in the entire cohort, including 6 AML de novo, 11 secondary and 2 MDS

[b] Results of the entire cohort of 65 high-risk AML-MDS patients, 55 AML including 13 relapsed/refractory patients and 43 untreated AML, 10 MDS and 30 unfavorable karyotypes

[c] Results of the entire cohort including: 23 R/RF AML with CR duration < 1 year, 5 R/RF AML with CR duration > 1 year, 40 and 15 untreated AML and MDS patients unfit for intensive chemotherapy, and 20 AML evolving from MDS, or relapsed/refractory MDS or myelofibrosis

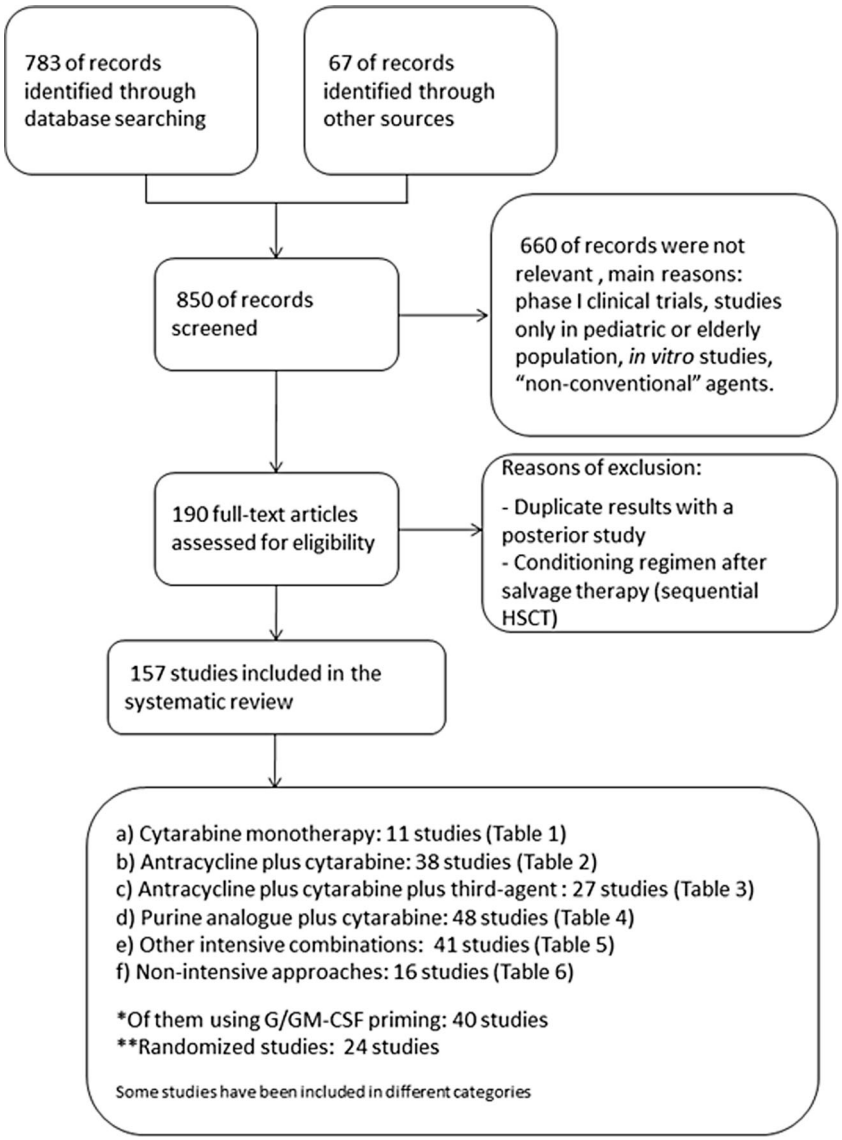

Fig. 1 Summary of evidence search and selection

106–110], the only two studies comparing both schemes did not show significant differences in CR, DFS, or OS [70, 86].

– Cladribine + Ara-C regimens

Six studies included schemes of cladribine and Ara-C, always combined with G-CSF (CLAG) [67, 89, 90, 111, 121], with the exception of one study with CLA [104]. The CLAG scheme showed wmCR rate of 45.5% (range 38–52%), wmCRD of 6 months (range 5.2–7.4), and wmOS of 6.8 months (range 5.6 to 7.9) [67, 89, 90, 111, 121].

– Fludarabine + Ara-C + idarubicin regimens (FLAG-IDA)

Eleven studies reported FLAG-IDA with Ara-C intermittent infusion [32, 91, 92, 95, 113–115, 118] or Ara-C in CI (CI-FLAG-IDA) [88, 94, 120]. The outcomes of FLAG-IDA schedule were better than CI-FLAG-IDA, showing higher CR rate (weighted mean 52.9%, range 42–69 vs. 34.3%, range 31–37%), mCRD (16, range 3.4–16.8 vs. 6.2, range 4–11.5 months) and mOS (8.4, range 6.7–11 vs. 4.1, range 2.5–5.6 months). On the other hand, a study using FLAG-IDA/FLAG/FLAG plus liposomal daunorubicin in seven relapsed AML patients after HSCT, reporting CR of 86% and mCRD and mOS of 14 months [113]. Besides, a recent large retrospective study comparing FLAG-IDA with FLAGO-IDA (adding GO) suggested equivalent results with both schemes in CR rate (50.4 vs. 60.5) and OS (8.4 months in both arms) [95].

– Fludarabine + Ara-C + mitoxantrone regimens

The MITO-FLAG scheme was reported in three studies [96, 97, 112], in two of them comparing the

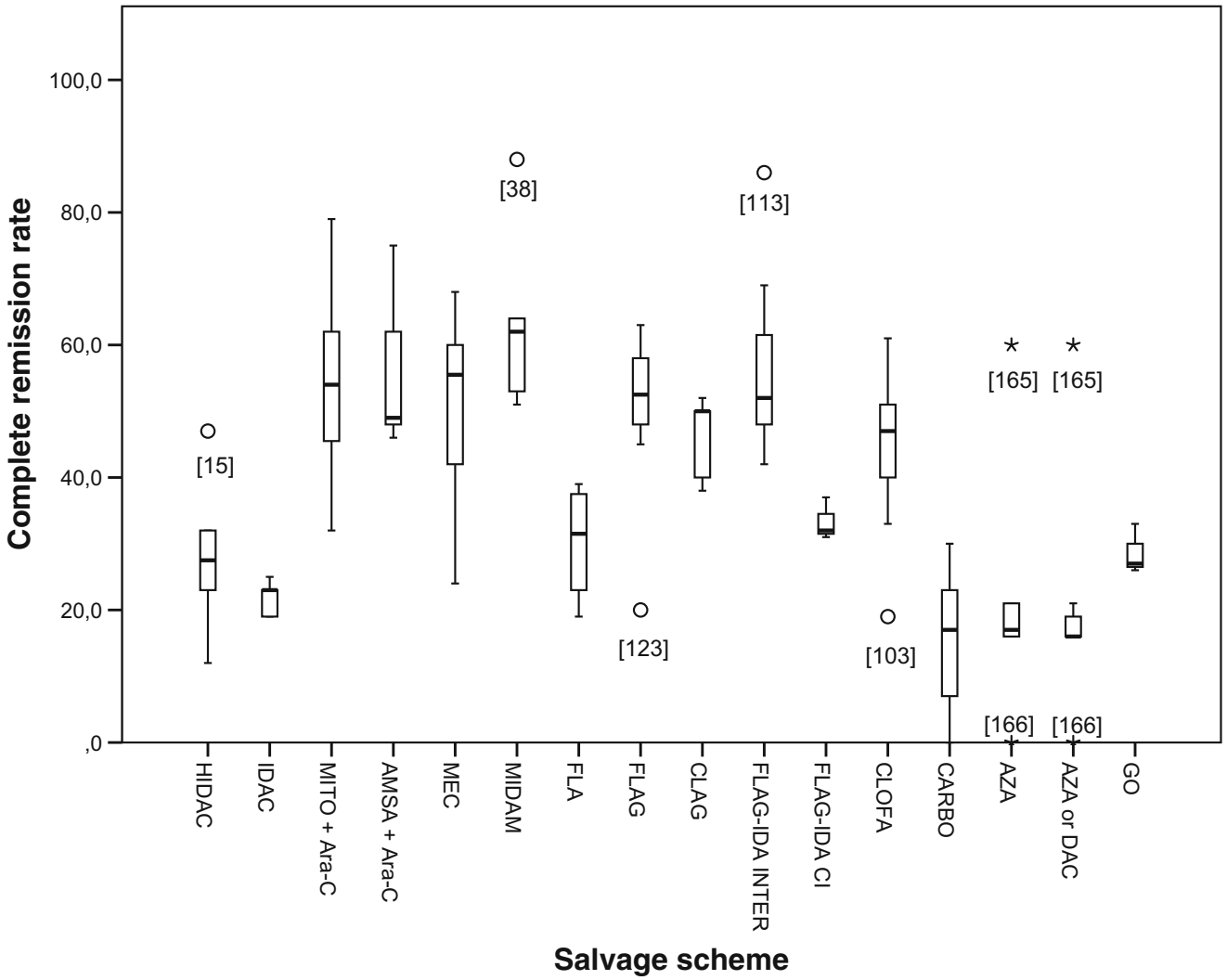

Fig. 2 Boxplot diagram of the complete remission rate of the different salvage therapies. The simple size for each scheme, excluding the outliers, was as follows: HIDAC 350; IDAC 686; MITO + Ara-C 801; AMSA + Ara-C 264; MEC 827; MIDAM 326; FLA 206; FLAG 402; CLAG 241; FLAG-IDA intermittent infusion 539; FLAG-IDA CI 135; CLOFA 369; CARBO 143; AZA 537; hypomethylating agents (AZA or DAC) 868; GO 462. The outliers are identified with the reference and two different markers: small circle for "out" values and asterisk for "far out" or "extreme values" (more than three times the height of the boxes)

administration in bolus and in CI of Ara-C [97, 112], with CR rates between 43 and 80% and mOS between 6.6 and 7.1 months. The significant improvement in CR rate of bolus infusion against CI observed in the first non-RCT [112] (80 vs. 43%), was not reproduced in a later RCT [97] (54 vs. 43%). The mOS of both arms in the two studies was similar (6.8 months in both arms [112] vs. 7.1 and 6.1 months [97]).

– Fludarabine + Ara-C + daunorubicin regimens

This combination was employed in three cohorts [98, 99, 119], showing CR rates ranged from 47 to 53% and mOS from 5.8 to 9 months. The most recent report combined this scheme with G-CSF [99], without significant differences with the previous outcomes observed (CR 53% and OS 9 months).

– Cladribine + Ara-C + mitoxantrone regimens

Four studies used the MITO-CLAG scheme (cladribine + Ara-C + mitoxantrone + G-CSF) [90, 100, 101, 121], showing CR rates of 39–58%, mCRD of 5.5 months (only reported in one study [121]) and mOS of 5.5–9 months. No clear differences were observed between CLAG and MITO-CLAG regimens in two comparative studies [90, 121].

– Fludarabine + Ara-C + other agent regimens

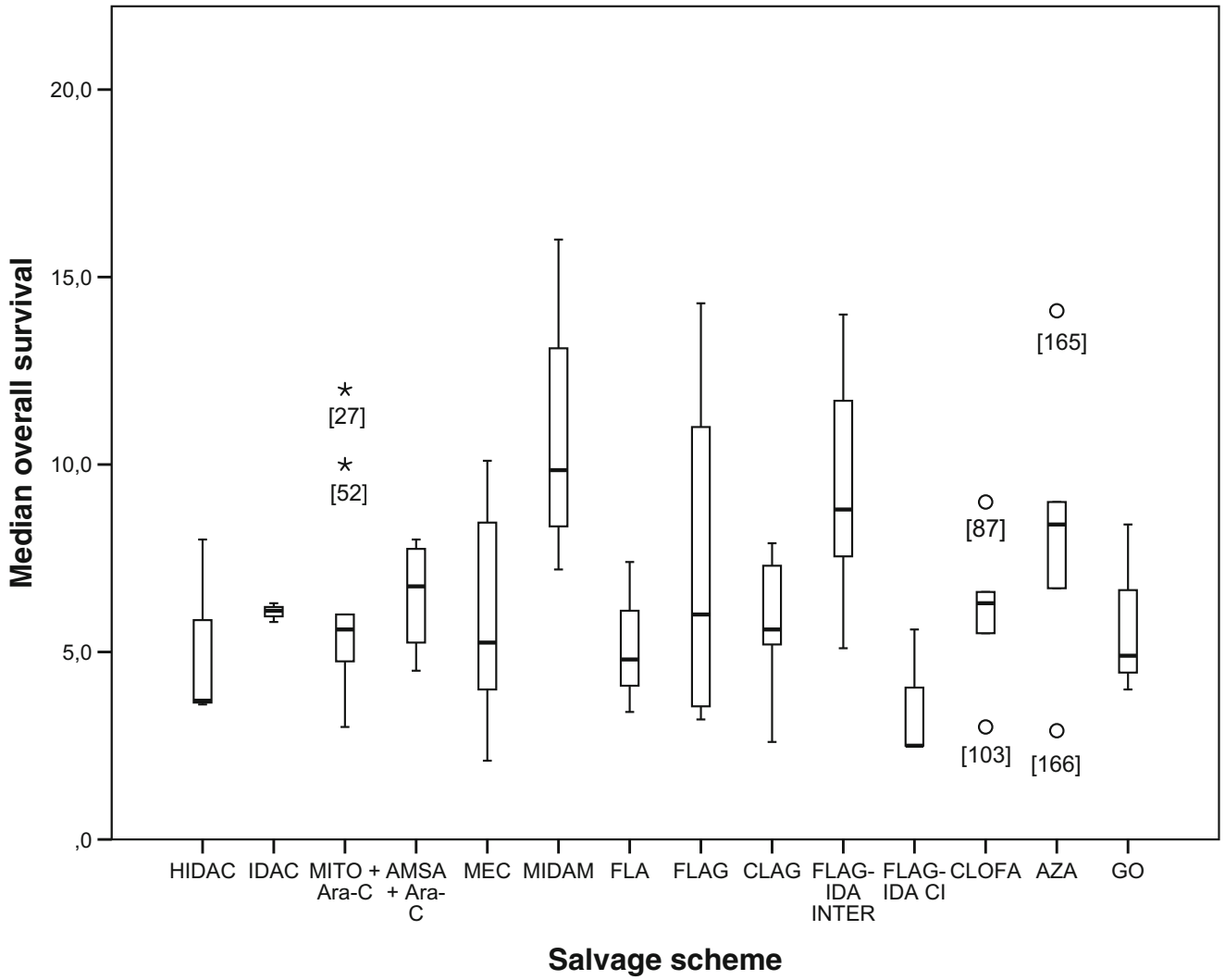

Fig. 3 Boxplot diagram of the median overall survival reported of the different salvage therapies. The simple size for each scheme, excluding the outliers, was as follows: HIDAC 248; IDAC 599; MITO + Ara-C 578; AMSA + Ara-C 172; MEC 536; MIDAM 188; FLA 147; FLAG 219; CLAG 221; FLAG-IDA intermittent infusion 527; FLAG-IDA CI 135; CLOFA 252; AZA 537; GO 358. The outliers are identified with the reference and two different markers: small circle for "out" values and asterisk for "far out" or "extreme values" (more than three times the height of the boxes)

Other combinations of fludarabine and Ara-C with a third component different from anthracyclines have been analyzed [85, 92, 116]. The scheme fludarabine, Ara-C, and topotecan obtained a CR rate of 35%, mCRD of 5.2 months, and mOS of 5.2 months [116]. Different combinations with GO obtained similar results in two studies [85, 92], with a CR rate of 27–29%, mCRD of 8.3 months, and mOS of 5–7.4 months. The addition of GO to FLAG [85] and FLAG-IDA [92] apparently did not improve the CR and OS in two non-RCT.

– Clofarabine + Ara-C regimens

Nine studies reported the use of clofarabine plus Ara-C schemes, obtaining a wmCR rate of 44.2% (range 9–55%), wmCRD of 7.6 months (range 3.2–10.6), and wmOS of 6.2 months (range 3–9) [21, 87, 102, 103, 105, 115, 117, 122, 169]. A dose-finding prospective trial combined clofarabine, Ara-C, and idarubicin with CR 48% and mCRD 10.6 months, whereas the combination of clofarabine and idarubicin showed CR 13% and mCRD 4.4 months [105]. The combination of clofarabine and Ara-C was compared with IDAC in a RCT, showing a significant increase in CR with the addition of clofarabine (35 vs. 18%), but the same OS (6.6 vs. 6.3 months) [21]. A retrospective study performed in a cohort of R/R AML patients who declined or were ineligible for a clinical trial showed lower efficacy outcomes than clinical trials with clofarabine alone or in combination with Ara-C (CR 11 vs. 19%; OS 3 months in both arms) [103].

Other intensive combinations

Other intensive chemotherapy combinations have been evaluated in R/R AML (Table 5) [16, 18, 20, 22, 23, 36, 38, 39, 90, 104, 105, 124–153].

– Monotherapies

Sixteen studies analyzed different monotherapies, in most of the cases of active components of effective combinations, obtaining modest outcomes, usually lower than standard intensive combinations [22, 23, 39, 104, 124–132, 148–150]. Monotherapies with anthracyclines obtained limited results, with CR rates of 13% with amsacrine [23], 16–26% with idarubicin [125], and 8–44% with mitoxantrone [23, 126, 127]. Five studies analyzed the efficacy of carboplatin monotherapy, showing wmCR of 15.7% (range 0–30%) and wmCRD of 3.6 months (range 3.5–6) [128, 129, 148–150]. Worse outcomes were reported with the monotherapy of cladribine, without achieving any CR in two different studies [104, 130].

Elacytarabine, an elaidic acid ester of Ara-C, was tested in two studies in R/R AML patients reporting CR rates from 23 to 44%, mCRD of 5.1 months and mOS from 3.5 to 4.7 months [131, 132]. The RCT by Roboz et al. did not show improvements in CR or survival in comparison to the investigator's choice control arm (HiDAC, MEC, FLAG, FLAG-IDA, decitabine, azacitidine, hydroxyurea, or supportive care) [131].

– Ara-C + other agents

Eight studies evaluated other Ara-C combinations [16, 18, 20, 36, 38, 90, 133, 151]. A RCT demonstrated that HiDAC plus native asparaginase was superior to HiDAC alone (CR rate 38 vs. 24%, and OS 7.9 vs. 3.6 months) in patients younger than 60 years [16]. The combination of Ara-C with etoposide showed CR rates from 38 to 56% [18, 133, 151]. In a RCT, HiDAC plus etoposide did not show significant improvements against HiDAC (CR 38 vs. 31%; OS 5.2 vs. 3.7 months). A later study reported higher CR rate of 56% with IDAC and etoposide [133].

Other combinations with Ara-C have been tested, such as laromustine showing higher CR than Ara-C monotherapy (35 vs. 19%), but no differences in mOS (4.2 vs. 5.8 months) [20]. Combinations of Ara-C plus GO were reported in two studies [36, 38], one of them was non-representative of R/R AML (only in CBF-AML) and was previously commented [38]. The other study compared Ara-C plus GO with Ara-C plus cyclophosphamide and topotecan, resulting both ineffective schemes (CR 12 vs. 4; OS 3.7 vs. 3.8 months) [36]. A recent publication reported the use of MEC followed by decitabine after 5 days break (priming) showing CR 31% and OS 4.9 months [90].

IDAC plus vosaroxin was evaluated in the largest RCT in R/R AML, demonstrating better CR rate than IDAC (CR 37 vs. 19%) [22]. The OS in the entire cohort showed a trend to higher OS in vosaroxin group (OS 7.5 vs. 6.1 months, $p = 0.06$), with a significant improvement among patients 60 years of age and older.

– Anthracyclines + other agents

These combinations have been tested in 12 studies [105, 127, 134–141, 152, 153]. Six non-comparative studies analyzed the use of anthracyclines with etoposide, mitoxantrone in 4 [134, 135, 152, 153] and aclarubicin in 2 [136, 137]. The outcomes observed in these small and relatively young cohorts were similar for mitoxantrone and aclarubicin (CR 16–45 and 24–40%; mCRD 3.5–15 and 0.8–7.5 months; mOS 3–8 and 3.2 months). A later study in only five patients obtained a CR of 60% with the addition of GO to mitoxantrone and etoposide scheme [138].

Combinations of anthracyclines and purine analogs without Ara-C were poorly studied [105, 139]. No patients obtained CR with the schemes of cladribine plus daunorubicin or cladribine monotherapy in a small cohort [139]. The scheme clofarabine plus idarubicin was noteffective either (CR 13%; mCRD 4.4 months) [105]. On the other hand, combinations of anthracyclines with a pyrimidine analog gemcitabine showed a CR rate of 11% with mCRD of 3 months [140].

Hypomethylating agents, decitabine, and azacitidine, in combination with anthracyclines were tested in two trials [127, 141]. Mitoxantrone plus azacitidine showed lower CR rates than the monotherapy with mitoxantrone (CR 15 vs. 28%) in a mixed cohort of acute nonlymphocytic leukemia (ANLL) and chronic myeloid leukemia in myeloid blast phase (CML-BP) [127]. The combination of decitabine with amsacrine or idarubicin showed CR rates of 27 and 45%, respectively [141].

– Carboplatin + other agents

The limited efficacy observed with carboplatin CI monotherapy was intended to be improved with the addition of other drugs in six different studies [142–147]. The combination with etoposide showed CR 40% [142], but in another study, no CR was observed in a cohort of seven patients [143]. The triple therapy with carboplatin CI, etoposide, and Ara-C was analyzed in two studies with contradictory results, showing CR rates from 12 [145] to 50% [144]. In vitro synergistic and additive effects between carboplatin and anthracyclines were tested in a RCT comparing the combination of carboplatin CI with idarubicin and mitoxantrone, obtaining similar results (CR 29 vs. 28%; OS 2 vs. 2.5 months) [146]. Finally, a quadruple therapy called MECA (mitoxantrone CI + etoposide + carboplatin CI +

Ara-C) achieved CR rate of 32% and mOS of 8.5 months [147].

Non-intensive approaches

Different non-intensive salvage therapies have been employed, especially for unfit patients (Table 6) [40, 103, 154–167].

– Ara-C non-intensive regimens

Low dose of Ara-C administered subcutaneously was tested in two different studies, in monotherapy [154] and combined with ATRA [155], in both cases with high CR rates (44 and 49%).

– GO monotherapy

Monotherapies of GO using different dosages (1.5 to 9 mg/m^2 administered 1 or 3 days) were tested in four non-RCTs in elderly patients [40, 156, 157, 164], showing a wmCR rate of 21.1% (range 26–33%), wmCRD of 6.1 months (range 5–11), and wmOS of 5.4 months (range 4–8.4). A large cohort treated with GO monotherapy did not obtain better OS at 6 weeks in comparison to a historical cohort treated with Ara-C CI and mitoxantrone (OS 89 vs. 95%), although GO showed significantly fewer total hospital days [40]. In a dose-finding trial in a small cohort of R/R AML the CR rate was 21%, with mCRD of 6 months and mOS of 2 months [164]. Similar results were observed in a large cohort treated with GO 9 mg/m^2 obtaining CR rate of 26%, mCRD 5.2 months and mOS of 4.9 months [156]. A slight increase in CR rate was reported in a cohort of first relapsed AML treated with fractionated GO 3 mg/m^2 × 3 days (CR of 33%), with mCRD 11 months and mOS 8.4 months [157].

– Clofarabine monotherapy

Only one study reported the use of clofarabine in monotherapy in R/R elderly patients, showing similar poor results than clofarabine combination with Ara-C (CR 11 vs. 19%; OS 3 months in both arms) [103].

– Hypomethylating agents

Five non-RCTs analyzed the role of azacitidine monotherapy in R/R AML patients [158–160, 165, 166], obtaining a wmCR rate of 16.9% (range 0–60%), wmCRD of 2.9 months (range 6–11.9), and wmOS of 7.3 months (range 2.9–14.1). Besides, two studies evaluated the use of decitabine monotherapy [160, 161]. The first published report in ten patients relapsed after HSCT showed 60% CR and mOS of 14.1 months) [165]. In a small cohort of 20 elderly patients, no CR was obtained and mOS was 2.9 months [166]. In two later large cohorts of elderly patients, the CR rates were 21 to 17%, with mCRD of 6–11.9 months and mOS of 8.4–9 months [158, 159]. These outcomes were reproduced in a large multicentric retrospective study showing a CR rate of 16% and mOS of 6.4 months in a cohort of 656 R/R AML patients treated with azacitidine or decitabine, without differences according to the agent [160]. Another study evaluated the employment of decitabine monotherapy and combined with GO with similar results (CR 16% in both arms; OS 7 months) [161].

A non-intensive combination of azacitidine, ATRA, and valproic acid was tested in a single study showing CR 15% and mOS 2.9 months [162]. Valproic acid demonstrated in vitro an additive or synergistic effect added to a DNA methyltransferase inhibitor such as azacytidine [170].

– Decitabine + GO regimens

The schedule decitabine plus GO in R/R AML was evaluated in three different studies [161, 163, 167]. This scheme obtained positive results in a small cohort (CR 46%; OS 6 months), probably related relatively young age of patients and because more than a half of patients were relapsed after HSCT, subgroup with better prognosis [167]. In a phase II study, the combination of decitabine and fractionated GO showed lower OS than decitabine alone (3.6 vs. 7 months) and CR rate of 16% combining both arms [161]. These results were reproduced in another elderly cohort, with CR/CRi rate of 24% and mCRD 5.8 months [163].

Role of priming

The role of priming with G-CSF in AML chemotherapy continues being controversial yet, including de novo AML [168, 171]. In 40 studies included in this review, the priming with G-CSF was part of the schedule [33, 34, 41, 54, 57, 59, 60, 63, 64, 67, 70, 83, 84, 86–97, 99–101, 106–114, 118, 120, 121]. Five studies of the anthracycline plus cytarabine-based regimens added hematopoietic growth factors. One of them combined Ara-C, mitoxantrone, and granulocyte-macrophage-CSF (GM-CSF) without a significant improvement [41]. On the other hand, four studies reported the use of CAG regimen (low dose Ara-C, aclarubicin, G-CSF) with positive results, but no RCT demonstrated the superiority of this approach [33, 34, 54, 57]. Six studies comparing a schedule of Ara-C, anthracyclines and etoposide with and without G-CSF or GM-CSF did not show any improvement by use of priming [34, 59, 60, 63, 64, 70].

Most of the studies with purine analogue plus cytarabine-based regimens employed G-CSF priming in their schedules, although the benefit of this strategy has not been clearly demonstrated [41, 67, 70, 83, 84, 86–97, 99–101, 106–114, 118,

120, 121]. Two studies compared the efficacy of FLA and FLAG schemes, one RCT [70] and one retrospective comparison [86], and in both cases, no differences were observed in any CR, DFS, and OS. Between CLA and CLAG schemes were not a direct comparison, but the only published study with CLA [104] showed lower efficacy than the five studies with CLAG [67, 89, 90, 111, 121]. In combinations including anthracyclines, such FLAG-IDA, MITO-FLAG, or MITO-CLAG, the G-CSF is always part of the standard treatment, and comparative studies analyzing the benefit of priming were not published.

Discussion

To our knowledge, this is the first systematic review analyzing the outcomes after salvage regimens using conventional chemotherapy agents in R/R AML patients. Leopold et al., published in 2002 a systematic review on this topic, but the authors only included AML patients at first relapse [172]. In addition, other authors have critically reviewed the literature on the R/R AML setting without a systematic search [173–175]. Our study selection included 157 out of 850 records, with a wide variety of schedules, revealing that there is still no recognized standard treatment in R/R AML. Several regimens have achieved relatively high CR/CRi rates, but none of them obtained outstanding CR duration or increased survival rates. In general, the reviewed manuscripts were retrospective analyses performed in small cohorts, with only few studies with high methodological quality, such as RCTs. Besides, there is a lack of evidence in the real-life population, and we can even raise the question on whether to administer or not any salvage regimen for a subset of patients with demonstrated poor prognosis (i.e., del 17p or P53mut [176], or unfit/vulnerable subjects). Furthermore, the high variability in the study design and the inclusion criteria makes challenging to perform comparisons between studies. This systematic review was restricted to explore the outcomes using only conventional chemotherapy agents, which are still the backbone of salvage regimens out of an experimental context. Nevertheless, to have a better understanding of the R/R ground, we included studies in R/R AML adult population at any disease stage (i.e., primary refractory as well as first relapse or beyond). Regarding the great heterogeneity among type of analyzed R/R patients, we note that (1) there are few data on outcomes of patients at second or beyond R/R episode [25, 28, 33, 46, 59, 61, 68, 84, 87, 97, 107, 115, 122, 125, 135, 141, 145, 146, 169], and (2) there is no consensus when referring to primary refractory disease (i.e., after 1 or 2 cycles of induction? should a PR after cycle 1 be considered as resistance?). In this regard, the recently published ELN guidelines recommend considering a primary refractory disease only after two induction cycles, irrespectively of the schedule used in the second cycle [1]. Although this recommendation could be useful to standardize definitions for clinical trials, they are not reflecting what has been considered in the clinical practice in the past decades.

A rational decision algorythm to recommend conventional salvage therapies versus experimental approaches (i.e., clinical trial or sequential allo-HSCT) could be using several prognostic factors related to dismal outcome under standard approaches [2–12], or even better using some of the available scoring systems to predict OS (e.g., scores by GOELAMS, PETHEMA, and HOVON) [76, 95, 177]. The main adverse factors included in those scoring systems were older age, shorter CR1 duration, unfavorable cytogenetics, mutated FLT3-ITD, and previous HSCT. In addition, significant lower CR rates were reported in R/R AML patients older than 60 years [3–7, 16, 178], as well as in those with shorter CR1 duration [3, 7–9, 178] and unfavorable karyotype [7, 10–12]. We observed in almost all studies better CR rate in LR (wmCR 58.2%) than ER patients (wmCR 31.1%), and refractory patients (wmCR 34.5%) [8, 17, 18, 22, 25, 31, 33, 47, 48, 58, 61, 69, 76, 83, 84, 86, 87, 95–97, 163, 169], but again, the inconsistency of the definitions for refractoriness and LR vs. ER, as well as the diversity of chemotherapy regimens applied, precludes from any clear statement. Interestingly, the CR rate reported in first R/R (wmCR of 50.8% in relapsed and 34.5% in refractory patients) versus ≥2ndR episodes (wmCR 49.2%) showed high variability, obtaining worse [28, 59, 61, 87, 122, 125, 135, 146], similar [33, 84, 169] or even better [25, 46, 59, 68, 97, 107, 115, 141, 145] responses in ≥2ndR patients. On the other hand, the HOVON group found worse outcomes in patients relapsing after HSCT, probably due to a higher cumulative toxicity, more aggressive leukemia, and less alternative therapies [177]. In contrast, our review reveals a wmCR of 59.8% in patients relapsing after HSCT, whereas the wmCR rates of relapsed and refractory patients were 53 and 47.5%, respectively [58, 68, 84, 95, 106, 107, 109, 113, 165, 167]. By the way, Bergua et al. explained the better CR and OS in first R/R episodes experienced after an allo-HSCT by the host immunosuppressive effect of FLAG-IDA [146], which could induce graft-versus-host/leukemia disease and full-donor chimerism [113, 179].

Regarding the weighted mean of CR and ED rates after intensive salvage regimens, in our opinion, this review shows that the following regimens have the more acceptable results: AMSA plus Ara-C (54.3 and 6.8%) [7, 27, 42, 44, 48, 49, 53], MEC (52.5 and 8.3%) [58–67, 79–82], MIDAM (59.4 and 5.7%) [38, 75–78], FLAG (53.3 and 8.7%) [8, 70, 83–86, 88, 106–110, 123], CLAG (45.5 and 9.4%) [67, 89, 90, 111, 121], FLAG-IDA intermittent infusion (52.9 and 13.4%) [32, 88, 91, 92, 94, 95, 113–115, 118, 120], and clofarabine plus Ara-C (44.2 and 14.3%) [21, 87, 102, 103, 105, 115, 117, 122, 169], while others apparently may offer suboptimal rates related to lower efficacy or higher toxicity, e.g., HiDAC (28 and 29%) [8, 15, 16, 18, 19, 23], mitoxantrone plus Ara-C (50 and

25.2%) [4, 5, 19, 25–29, 39–41, 43, 46, 47, 50–52], iDAC (20.6 and 12.8%) [8, 17, 20–22], and hypomethylating agents (16.5%, ED not reported) [158–161, 165, 166]. However, despite better CR rates with some optimal regimens, the OS and mCRD obtained with these schemes remain disappointing like others (overall wmOS ranging from 6.2 to 8.7 months, and wmCRD from 4.8 to 9.8 months). The combinations with better long-term results were FLAG-IDA intermittent infusion (wmOS 8.4 months and wmCRD 16 months) [32, 88, 91, 92, 94, 95, 113–115, 118, 120] and MIDAM (wmOS 12.6 months) [38, 75–78]. The possible causes of these poor post-remission outcomes includes the poor quality of the response, the very high rate of relapse (especially when an allo-HSCT is not performed), and the high toxicity-related mortality (especially after a subsequent allo-HSCT).

There is few evidence to select a standard regimen in R/R AML, with only few RCTs published so far, some of them comparing the experimental arm with suboptimal controls (e.g., iDAC)(Supplemental Table 1). Furthermore, the ELN [1] and NCCN [180] clinical guidelines recommend some salvage schemes with scarce supporting literature (e.g., CLAG + mitoxantrone or idarubicin [90, 100, 101, 121], clofarabine ± Ara-C + G-CSF ± idarubicin [21, 87, 102, 103, 105, 115, 117, 122, 169]), or with suboptimal CR rates (e.g., HiDAC [8, 15, 16, 18, 19, 23] or iDAC [8, 17, 20–22]). We can raise criticism about these suggested regimens if we aim to achieve a CR to undergo an allo-HSCT. However, these schedules are acceptable if we aknowledge that other regimens achieving "optimal CR" rates did not improve mOS. Actually, a recent retrospective study [181] showed higher CR rate with intensive salvage regimens (Ara-C + anthracyclines, MIDAM or FLAG-IDA) than iDAC scheme (employed as control arm in recent RCTs [21, 22]) (53 vs. 19%), but similar OS (8 vs. 6.1 months). Given these data, we can raise the question about the most relevant study endpoints for R/R AML trials. Although the OS from the initiation of salvage therapy is commonly used, the EFS could be more appropriate to test the efficacy and safety of any regimen. In addition, at least in fit R/R AML patients, the rate of CR/CRi and the feasibility of a subsequent allo-HSCT should be considered as secondary endpoints. Regarding the use of priming with growth factors in R/R AML, it has been widely studied, with contradictory results [33, 34, 41, 54, 57, 59, 60, 63, 64, 67, 70, 83, 84, 86–97, 99–101, 106–114, 118, 120, 121].

There is a consensus to perform an allo-HSCT after the salvage regimen in order to improve the long-term outcomes, although the OS at 4 years does not exceed 20–30% in patients successfully bridged to transplant in CR [182, 183]. Besides, the AMLSG group analyzed the impact of allo-HSCT after first induction failure in 875 patients, showing significant differences in OS at 5 years between allo-HSCT in first CR (48%), direct allo-HSCT (36%) and allo-HSCT in refractory disease after salvage therapy (25%) [184]. Nevertheless, the allo-HSCT option will not be feasible in the majority of patients, by absence of suitable donor or due to limiting comorbidities, especially in old patients. The therapeutic options in elderly unfit patients are limited to non-intensive approaches aiming to control disease progression and minimize treatment-related mortality. In fact, this subset represents the majority of R/R AML patients, for whom the last update of NCCN guidelines [180] recommended hypomethylating agents or low-dose Ara-C, both with a low level of evidence.

Some limitations of this review should be addressed. First, the variability of the definitions of CR rate, R/R and the changes in the laboratory analyses could difficult the comparisons between studies with more than 30 years in the date of publication. Second, the differences in methodology and patient selection of the studies could influence in efficacy reported and it should be interpreted with caution. Third, heterogeneity of the disease between R/R patients, as well as between ER, LR or relapse after HSCT, can mask the real effect of a salvage therapy in a specific subset of patients when it was reported together. Fourth, the impact of prognosis factors (age, performance status, FLT3-ITD or dmCEBPA mutations, etc.) has not been measured in this review, in most of the cases for lack of information in the original articles. Finally, the methodological quality of the majority of the studies included is low, with only a few RCTs.

In conclusion, R/R AML in adult patients is a major challenge. Salvage therapies with conventional antileukemic agents have been employed for decades, none of them achieving outstanding CR rates, long-lasting remissions and acceptable OS. A better knowledge of the prognostic factors, more effective and less toxic combinations using conventional and new therapies, as well as improvements in allo-HSCT procedure and timing, could play a role to improve the clinical outcomes in the future. In our opinion, clinical trials should be the first treatment option in R/R AML, both in fit and unfit patients. In this regard, the PETHEMA group is planning a trial in R/R AML patients, which incorporates a Precision Medicine test to select the salvage regimen according to the ex vivo leukemic sensitivity to conventional chemotherapy agents [185].

Acknowledgements We are grateful to Vivia Biotech for an educational grant that supported this study.

Compliance with ethical standards

Conflict of interest The authors declare that they no competing interests.

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