**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** | | | | | | | | | |
| Link et al. 1990 [59] | RCT, Phase II, MC, 2-Arms | **MAV-A:** Ara C (100 mg/m2 d:1-5) + MITO (10 mg/m2 d:1-5) + ETOP (100 mg/m2 d:1-5)  or  **MAV-B:** Ara C (100 mg/m2 d:1-8) + MITO (10 mg/m2 d:4-8) + ETOP (120 mg/m2 d:4-8) | 16  (16 R or RF)  20  (20 R or RF) | 51 (20-73) in both arms | CR: 9 (56)  ED: 1 (6)  CR: 12 (60)  ED: 4 (20) | 4.5 m in both arms | 5.5 m in both arms | mEFS: 4.5 m in both arms | NA |
| Amadori et al 1991 [60] | Non-RCT, RETROSP, MC, 1-Arm | **MEC:** Ara C (1 g/m2 d:1-6) + MITO (6 mg/m2 d:1-6) + ETOP (80 mg/m2 d: 1-6). | 32  (14 R, 18 RF) | 24 (5-56) | CR: 21 (66)  ED: 2 (6) | 3.7 m | 8.4 m | NA | 4 (13) HSCT, 3 allo-HSCT & 1 auto-HSCT |
| Tribalto et al. 1991 [61] | Non-RCT, PROSP, Phase II, UC, 1-Arm | Ara C (200 mg/m2 d:1-5) + MITO (7 mg/m2 d:1-3) + ETOP (150 mg/m2 d: 1-3) | 5  (3 R, 2 RF) | 63 (17-78)a | CR: 3 (60)  In RF, CR: 0 (0)  In R, CR: 3 (100)  ED: 1 (20) | 6.3 ma | 3 ma | NA | NA |
| Spadea et al. 1993 [63] | Non-RCT, RETROSP, Phase II, UC, 1-Arm | Ara C (1 g/m2 d:1-6) + MITO (6 mg/m2 d:1-6) + ETOP (80 mg/m2 d: 1-6) | 58  (5 ER, 15 LR, 10 R HSCT, 28 RF) | 36.7  (4.5-60.6)b | 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 [64] | Non-RCT, PROSP/RETROSP, MC, 2-Arm | Ara C (500 mg/m2 d:1-3, 8-10) + MITO (12 mg/m2 d:1-3) + ETOP (200 mg/m2 d: 8-10) + GM-CSF (5 µg/kg d:4-8)  or  Ara C (500 mg/m2 d:1-3, 8-10) + MITO (12 mg/m2 d:1-3) + ETOP (200 mg/m2 d: 8-10). Historical cohort | 20  (14 R, 3 RF, 3 ≥2ndR)  38  (23 R, 12 RF, 3 ≥2ndR) | 43 (20-60)  41 (16-60) | CR: 6 (30)  In RF, CR: 0 (0)  In R, CR: 4 (29)  In ≥2ndR, CR: 2 (66)  ED: 3 (15)  CR: 16 (43)  In RF, CR: 3 (25)  In R, CR: 12 (52)  In ≥2ndR, CR: 1 (33)  ED: 3 (8) | NA | 2.1 m  4.3 m | mDFS 1.1 m  mDFS 3.5 m | NA |
| Ohno et al. 1994 [66] | RCT, Phase III, MC, double-blinded, 2-Arms | Ara C (200 mg/m2 d:1-7) + MITO (7 mg/m2 d:1-3) + ETOP (100 mg/m2 d:1-5) + G-CSF (200 µg/m2 d:-1-33)  or  Ara C (200 mg/m2 d:1-7) + MITO (7 mg/m2 d:1-3) + ETOP (100 mg/m2 d:1-5) + placebo | 24  (19 R, 3 RF, 2 ≥2ndR)  26  (16 R, 3 RF, 7 ≥2ndR) | 43 (18-63)  47 (16-66) | CR: 13 (54)  ED: 0 (0)  CR: 11 (42)  ED: 2 (8) | NA | NA | NA | NA |
| Archimbaud et al 1995 [67] | Non-RCT, PROSP, MC, 2-Arm | **EMA-86:** Ara C (500 mg/m2 d:1-3, 8-10) + MITO (12 mg/m2 d:1-3) + ETOP (200 mg/m2 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 & 13 auto-HSCT |
| Vignetti et al 1996 [68] | Non-RCT, PROSP, Phase II, UC, 1-Arm | **MEC:** Ara C (1 g/m2 d:1-6) + MITO (6 mg/m2 d:1-6) + ETOP (80 mg/m2 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 & 1 allo-HSCT |
| Thomas et al. 1999 [69] | RCT, Phase III, MC, double-blinded, 2-Arms | **EMA-94:** Ara C (500 mg/m2 d:1-3, 8-10) + MITO (12 mg/m2 d:1-3) + ETOP (200 mg/m2 d: 8-10) + GM-CSF (5 µg/kg d:4-8)\* 1-2 courses  or  Ara C (500 mg/m2 d:1-3, 8-10) + MITO (12 mg/m2 d:1-3) + ETOP (200 mg/m2 d: 8-10)+ placebo \* 1-2 courses | 95  (36R, 59 RF)  97  (36 R, 61 RF) | 47 (17-65)    46 (16-65) | CR: 62 (65)  In RF, CR: 30 (51)  In R, CR: 32 (89)  ED: 5 (5)  CR: 57 (59)  In RF, CR: 28 (46)  In R, CR: 29 (81)  ED: 8 (8) | 5.1 m  3.8 m | 10.1 m  8.5 m | mDFS 8.4 m  mDFS 8 m | 18 (19) HSCT, 9 allo-HSCT & 9 auto-HSCT  14 (14) HSCT, 9 allo-HSCT & 5 auto-HSCT |
| Thomas et al. 2000 [70] | Non-RCT, PROSP, Phase I/II, MC, 3-Arms | **EMA:** Ara C (500 mg/m2 d:1-3, 8-10) + MITO (36 mg/m2 or 45 mg/m2 or 60 mg/m2 d:1) + ETOP (200 mg/m2 d: 8-10)\* 1-2 courses | 24  (21 R, 3RF) | 48 (19-64) | CR: 16 (67)  ED: 1 (4) | 1.5 m | 9.6 m | NA | 6 (25) allo-HSCT |
| Revesz et al. 2003 [72] | Non-RCT, RETROSP, UC, 1-Arm | **EMA:** Ara C (500 mg/m2 d:1-3, 8-10) + MITO (12 mg/m2 d:1-3) + ETOP (200 mg/m2 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 & 1 auto-HSCT |
| Lee et al. 2006 [74] | Non-RCT, PROSP, Phase II, UC, 1-Arm | Ara C (1 g/m2/24h CI d:1-5) + MITO (12 mg/m2 d:1-3) + ETOP (150 mg/m2 d: 1-3)\* 1-2 courses | 33  (14 R, 16 RF, 3 ≥2ndR) | 34 (20-59) | CR: 17 (52) | 3.9 m | 7.3 m  OS at 3 y: 6% | NA | 5 (15) allo-HSCT |
| Lee et al. 2009 [77] | Non-RCT, PROSP, Phase II, UC, 2-Arms | Ara C (1 g/m2/24h CI d:1-5) + MITO (12 mg/m2 d:1-3) + ETOP (150 mg/m2 d: 1-3)\* 1-2 courses (cohort from Lee 2006 [74])  or  **CME2:** Ara C (1 g/m2/24h CI d:1-5) + MITO (36 mg/m2 d:1) + ETOP (150 mg/m2 d: 1-3)\* 1-2 courses | 33  (14 R, 19 RF)  25  (19 R, 6 RF) | 34 (20-59)  44 (19-68) | CR: 17 (52)  CR: 6 (24) | 3.9 m  3.7 m | 7.3 m  OS at 3 y: 6%  3.7 m | NA | 4 (12) allo-HSCT  1 (4) allo-HSCT |
| Price et al. 2011 [78] | Non-RCT, RETROSP, UC, 2-Arms (see table 4) | **MEC:** + Ara-C (1 g/m2 d:1-5) + MITO (8 mg/m2 d:1-5) + ETOP (100 mg/m2 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 [65] | Non-RCT, PROSP, Phase II, MC, 1-Arm | Ara C (600 mg/m2 d:1-5) + IDA (6 mg/m2 d:1-5) + ETOP (150 mg/m2 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 & 2 auto-HSCT |
| **Ara C + DNR + ETOP regimens** | | | | | | | | | |
| Liu Yin et al. 2001 [71] | RCT, MC, 2-Arms | **ADE 10+3+5:** Ara C (100 mg/m2/12h d:1-10) + DNR (50 mg/m2 d: 1, 3, 5) + ETOP (100 mg/m2 d: 1-5)\* 1 course; + ADE 8+3+5 \*1-2 courses  or  **Sequencial ADE:** Ara C (2 g/m2/12h d:1-3) + DNR (50 mg/m2 d: 1-3) + ETOP (200 mg/m2 d:8-10)\*1,2 courses | 85  (40 ER, 24 LR, 21 RF)  85  (42 ER, 25 LR, 18 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)  CR: 28 (33)  In RF, CR: 6 (33)  In R, CR: 22 (34)  ER, CR: 10 (24)  LR, CR: 13 (52)  ED: 20 (24) | NA | OS at 3 y: 12%  OS at 3 y: 6 % | DFS at 3 y: 22%  DFS at 3 y: 14% | 29 (17) HSCT, 19 allo-HSCT & 10 auto-HSCT |
| Milligan et al. 2006 [75] | RCT, MC, 2-Arms  (see table 4) | **ADE 10+3+5:** Ara C (100 mg/m2/12h d:1-10) + DNR (50 mg/m2 d: 1, 3, 5) + ETOP (100 mg/m2 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 & ATRA | NA | OS at 4 y: 27%  No impact of  G-CSF & ATRA | DFS at 4 y: 29%  No impact of G-CSF & ATRA | 31 (25) HSCT, 22 allo-HSCT, 9 auto-HSCT |
| **Ara C + AMSA + ETOP regimens** | | | | | | | | | |
| Sung et al. 2005 [73] | Non-RCT, PROSP, Phase II, UC, 1-Arm | Ara C (1 g/m2/12h d:1-3) + AMSA (100 mg/m2 d:1-3) + ETOP (100 mg/m2 d: 1-5) | 29  (23 R, 6 RF) | 35 (15-65)c | CR: 13 (45)  ED: 5 (17) | NA | 5 mc | mDFS 1.5 mc | 11 (38) HSCT, 9 allo-HSCT & 2 auto-HSCT |
| **Ara C + ACLA + ETOP regimens** | | | | | | | | | |
| Zhang et al. 2013 [54] | RCT, MC, 2-Arms (see table 2) | **E-CAG:** Ara C (10 mg/m2/12h SC d:1-14) + ACLA (14 mg/m2 d:1-4) +ETOP (30 mg/m2 d:1-4) G-CSF (200 µg/m2 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 [79] | Non-RCT, PROSP, UC, 1-Arm | Ara C (100 mg/m2 d:1-5) + ACLA (12 mg/m2 d: 1-5) + DAC (15 mg/m2 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 [58] | Non-RCT, PROSP, UC, 1-Arm | Ara C (500 mg/m2/12h d:3-8) + DOX (50 mg/m2 d:1) + VINCRISTINE (1 mg/m2 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 [62] | Non-RCT, RETROSP, UC, 1-Arm | Ara C (1 g/m2 d:8-14) + MITO (6 mg/m2 d:8-14) + DACARBAZINE (800 mg/m2 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 [76] | Non-RCT, RETROSP, MC, 1-Arm | **MIDAM:** Ara C (1 g/m2/12h d:1-5) + MITO (12 mg/m2 d:1-3) + GO (9 mg/m2 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 [80] | Non-RCT, RETROSP, MC, 1-Arm | **MIDAM:** Ara C (1 g/m2/12h d:1-5) + MITO (12 mg/m2 d:1-3) + GO (9 mg/m2 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 |
| Hospital et al. 2014 [56] | Non-RCT, RETROSP, MC, 2-Arms (see tables 2 & 5) | GO (6 to 9 mg/m2 d:1 or 3 mg/m2 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 & 3 auto-HSCT |
| Peterlin et al. 2016 [81] | Non-RCT, RETROSP, UC, 2-Arms | **S-MIDAM:** Ara C (1 g/m2/12h d:1-5) + MITO (12 mg/m2 d:1-3) + GO (9 mg/m2 d:4)  or  **F-MIDAM:** Ara C (1 g/m2/12h d:1-5) + MITO (12 mg/m2 d:1-3) + GO (3 mg/m2 d:1, 4, 7) | 15  (14 R, 1 RF)  18  (11 R, 7 RF) | 55 (9-70)  52 (26-70) | CR: 8 (53)  CR: 11 (61) | NA | 7.2 m  10.2 m | NA | 6 (40) allo-HSCT  12 (67) allo-HSCT |
| Hütter-Krönke et al. 2016 [82] | Non-RCT, PROSP, Phase II, MC, 1-Arm | **GO-A-HAM:** Ara C (3 g/m2/12h d:1-3) + MITO (12 mg/m2 d:2-3) + GO (3 mg/m2 d:1) + ATRA oral (45 mg/m² d:4-6; 15 mg/m² 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 |

**Abbreviations.** ≥2ndR: 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 acute non-lymphocytic leukemia (ANLL) poor- risk cohort, including 10 *de novo* leukemias (4 greater than 65 yrs 3 with cardiomyopathy); 12 secondary leukemias (5 secondary to a MDS, 5 to myeloproliferative syndrome, 2 to other neoplasias); 3 R; 2 RF.

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

C Results of the entire 51 AML/ALL R/RF cohort, including 29 AML & 21 ALL patients.

OS & CR has been estimated in months in the cases that it was reported in days (1 month = 30 days) & weeks (1 month = 4.3 weeks)