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Benchmarking treatment effects for patients over 70 with acute myeloid leukemia: A systematic review and meta-analysis

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Abstract

Objectives: The majority of patients with acute myeloid leukemia (AML) are aged 70 and over. However, there is uncertainty about how and whether older patients with AML should receive cytotoxic treatment.

Materials and methods: Medline and Cochrane library search was performed for studies in newly diagnosed AML which enrolled at least 20 patients per arm (for randomized controlled trials), or 50 patients (for non-randomized studies) over the age of 70. References were hand searched for additional eligible studies. Study investigators were contacted to maximize relevant data. Dual independent data extraction was done using standardized data collection forms. Data was collected on study and treatment characteristics, baseline patient information, and outcomes. Study methodological quality was assessed. The primary outcome was 1 year overall survival (OS). Impact of treatment [intensive chemotherapy (INT), low-dose chemotherapy (LOW), hypomethylating agents (HMA), or best supportive care (BSC)], cytogenetics, performance status, and comorbidity were assessed.

Results: The search produced 11,846 references of which 38 randomized controlled trials and 30 non-randomized studies met inclusion criteria, representing 13,381 patients, with a worldwide distribution. One-year OS with INT was 37% (31–42%), with LOW 11% (6–18%), with HMA 35% (18–54%) and with BSC 17% (13–21%). Two-year OS was 22% (18–26%), 11% (7–15%),

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Authorship

ME, JL, BD, and JK contributed to the design of the study. All authors contributed to the collection of the data, the data analysis, and the writing of the article.

Declaration of Competing Interest

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22% (16–28%), 6% (2–12%), respectively. We present subgroup data based on the studies including cytogenetics, performance status, and comorbidity. Formal direct comparisons with adjustment for all prognostic factors were not possible.

Conclusions: In this largest to date series of AML patients aged 70 and older, we provide benchmarks for treatment efficacy and effectiveness that may be used for decision analysis models and for the future development of clinical trials focusing on these patients.

Keywords

Acute myeloid leukemia; Older adults; Systematic review; Intensive chemotherapy; Hypomethylating agents; Low-dose chemotherapy; Best supportive care; Cytogenetics; Functional status; Comorbidity

1. Introduction

Over 20,000 patients per year are diagnosed with acute myeloid leukemia (AML) in the US [1]. The majority, 55%, are over the age of 70 at diagnosis [2]. While the 5-year survival of younger AML patients has more than doubled in the last four decades, the survival of older patients remains dismal with no reported progress over time [3,4]. A number of treatment alternatives exist, ranging from chemotherapy to hypomethylating agents to supportive care. However, the experts in the field disagree on how and whether older patients with AML should be treated at all, as it is unclear which treatment option has best benefit versus harms profile [5–7]. Population registries provide limited therapeutic and prognostic information, and review articles have identified a limited numbers of studies. Most papers define older as age 60 and over (e.g. [5,8]). Yet there are significant differences in the ability of a population of patients in their sixties and those in their seventies or eighties to tolerate chemotherapy or transplant. Most evidence appears to be observational and even though AML is a disease of older adults, they are underrepresented in randomized trials (RCTs). Therefore, one of the reasons for the seeming lack of progress in AML therapies for patients aged 70 and over seems to be related to insufficient testing of new treatments in clinical studies. However, a comprehensive evaluation of efficacy and effectiveness i.e. overall clinical research efforts in developments and testing of new treatments for older patients with AML has not been undertaken to date. Such undertaking is important for clinical and pharmaceutical researchers as it can serve as a benchmark for new drug developments. Similarly, both patients and clinicians can benefit from understanding the quality of existing evidence in the management of patients with AML, as well as clinical outcomes such as survival, response-rates, or treatment-related mortality. Accordingly, the purpose of this systematic review was to identify and describe all available studies in newly diagnosed patients with AML which enrolled and reported outcomes specifically for patients over 70 years of age, and included querying investigators for specific prognostic subgroup data.

2. Methods

2.1. Search and study selection

A comprehensive search of Medline and the Cochrane library was performed from inception to November 15, 2016 using the search strategy in Appendix Table 1. Two independent

authors reviewed all titles and abstracts and full texts of relevant references. Any disagreements between the two authors were resolved in consensus with a third author. References of included studies and relevant reviews were hand searched for additional eligible studies.

2.2. Inclusion criteria

All studies in newly diagnosed AML (non M3) that enrolled a significant proportion of patients over the age of 70 and had available outcome data were included in this systematic review. Both RCTs and non-randomized studies (NRS) were eligible. A valid subgroup of older patients was defined as enrolling at least 20 patients per arm over 70 years of age for RCTs and at least 50 patients over the age of 70 for NRS (considering that cohort studies report more heterogeneous populations). RCTs provide data on efficacy (i.e. assessment of treatment effect under the idealized circumstances of the study eligibility criteria) while NRS provide data on effectiveness (i.e assessment of effects of treatment in a real-life setting). No exclusions were made based on language or setting. The study selection process is reported according to PRISMA guidelines [9].

2.3. Data collection

Dual independent data extraction was done using a standardized data collection form. Data was collected on study characteristics, baseline patient information, treatment characteristics, and outcomes of patients over 70 years of age. Methodological quality of included studies was assessed using the Cochrane Risk of Bias Assessment tool for RCTs and the Newcastle-Ottawa scale for non-randomized studies [10,11].

In the case when studies enrolled a significant number of older patients but did not report outcome data for this subgroup, the original study investigators were contacted. Investigators were given the option to provide us with individual patient data or to complete a structured summary data collection form. When investigators were unable to provide any outcome data specific to the older population (over 70 years of age), the studies were excluded from the review.

2.4. Classification of treatments

To allow group analysis, studies were classified in four treatment categories. The categories were strictly defined prior to data collection and were 1) intensive chemotherapy which included standard anthracycline + cytarabine ("3 + 7") regimens or equivalents, 2) low-dose chemotherapy, 3) hypomethylating agents which included any regimens incorporating azacitidine or decitabine, and 4) best supportive care which also included hydroxyurea and single agent experimental drugs which ultimately did not demonstrate survival advantage. The regimens were classified independently by two authors and discussed at formal consensus meetings by all authors.

2.5. Analysis

High heterogeneity between included studies and lack of head to head comparisons limited our ability to conduct a robust comparative meta-analysis. Therefore, we largely undertook a descriptive systematic review. For network plots, we used NETPLOT [12]. Additionally, we

conducted a proportional meta-analysis by treatment modality using METAPROP_ONE [13]. This was deemed important to provide the average outcomes that can be achieved in the treatment studies of AML (“benchmarks”), which, in turn, can inform the design of future clinical trials. Because one, two, and three year survival are commonly accepted metrics in the design of AML trials, we also summarized these outcomes (instead of expressing mortality or survival via pooled summary statistics such as hazard ratio (HR)). While this approach is informative, it includes necessary bias as the analysis did not take into account the effects of censoring, missing data and difference in follow-up times among trials. Similar consideration applies to the subgroup analyses.

A sensitivity analysis was performed by study design (RCT versus NRS) and by prognostic variables: Eastern Cooperative Group (ECOG) performance score (0–1 versus > 1), cytogenetics (Favorable+Intermediate versus Poor, as classified by each study), AML type (De novo versus Secondary), and Charlson Comorbidity Index (no comorbidities versus 1 or more comorbidity). Subgroups which contained data on less than 10 patients were excluded from analysis. All analyses were performed using STATA 14 [14].

The study was approved by the Institutional Review Board of the University of South Florida.

3. Results

3.1. Study selection

The study selection process is reported in Fig. 1. Briefly, the search produced 11,846 references of which 77 RCTs and 81 NRS met initial inclusion criteria for significant number of newly diagnosed older patients with AML enrolled. After contacting original investigators, 38 RCTs [15–53] (6419 patients) and 30 NRS [3,54–82] (6962 patients) had data available for patients over 70 years of age and were included in the systematic review and meta-analysis. Source of data included in the systematic review is presented in Table 1.

3.2. Study characteristics

A summary of study characteristics is presented in Table 2. Among the included studies, 19% (5/38 RCTs and 8/30 NRS) [27,30–32,34,61,64,65,70,75,78,79,81] enrolled only patients over the age of 70 while the remaining 55 studies enrolled a mix of younger and older patients. The majority of studies, 82% (30/38 RCTs and 26/30 NRS) studied an intensive regimen on at least one arm of the study [3,15,17–21,23,25,26,28,29,34–45,47–51,53–70,72,75,76,78–82]. Low dose chemotherapy was studied in 15% of studies (4/38 RCTs and 6/30 NRS) [22,24,33,46,54,60,65,66,78,80], hypomethylating agents were studied in 7% of studies (1/38 RCTs and 4/30 NRS) [33,55,56,60,74,77], and best supportive care was studied in 24% of studies (6/38 RCTs and 10/30 NRS) [3,16,22,24,27,30,32,54–56,60,61,64,65,71,73,82]. The majority of the included studies were multicenter and included a mixed age population. Their publication dates ranged from 1984 to 2016 with the majority of studies published after 2000 (Appendix Fig. 1). The individual characteristics of each included study are reported in Appendix Tables 2 and 3.

3.3. Methodological quality of included studies

Overall, the risk of bias in most included studies was low. Risk of bias for individual studies is reported in Appendix Tables 4 and 5. Among the RCTs 68% (26/38) had low risk of randomization bias and 53% (20/38) had low risk for allocation concealment. The remaining studies did not report randomization procedures used. Most studies were open label, however the bias was deemed low risk due to the majority of studies having objective outcomes such as death. All studies had low attrition bias and one study had a high risk of reporting bias. Among the NRS, 7 studies utilized prospective design while 23 studies were retrospective. The majority, 60% (18/30), of studies reported on a representative cohort of patients while the source of patient population was unclear in 40% (12/30) studies. All studies relied on secure medical records for data collection and had adequate follow-up.

The average sample size in RCTs was 167 and ranged from 40 to 631. Among the NRS, the average sample size was 231 and ranged from 25 to 2748.

3.4. Direct comparisons studied

The network diagram for included studies is presented in Fig. 2. Of the included RCTs two studies (488 older patients) [22,24] evaluated low-dose therapy versus best supportive care and one study (344 older patients) evaluated low dose therapy versus hypomethylating agents [33]. The 30 RCTs (4392 older patients) that evaluated intensive therapies did all randomize between two or more intensive regimens [18–21,23,25,26,28,29,31,34–45,47–51,53]. Additionally one RCT (119 older patients) studied only low-dose regimens [46], and four RCTs (1076 older patients) studied only best supportive care [16,27,30,32]. It is important to note that no eligible study compared intensive therapy to other treatment modalities in the older population.

Among the NRS, intensive care was compared to best supportive care in eight studies (3654 older patients) [3,54–56,60,61,64,65,82], low-dose therapy in six studies (658 older patients) [54,60,65,66,78,80], and hypomethylating agents in two studies (357 older patients) [55,56,60]. Low dose therapy was compared to hypomethylating agents in one study (94 older patients) [60] and best supportive care in three studies (455 older patients) [54,60,65]. Hypomethylating agents were compared to best supportive care in two studies (362 older patients) [55,56,60]. In all, 15 NRSs (2414 older patients) evaluated only intensive therapies [57–59,62,63,67–70,72,75,76,79,81], two NRS (185 older patients) evaluated only hypomethylating agents [74,77], and two studies (123 older patients) evaluated only best supportive care [71,73].

Studies reporting data by various risk categories are presented in Appendix Fig. 2.

3.5. Outcomes

As mentioned above, the data could not support a formal comparative meta-analysis. Proportional data are summarized in Table 3 by treatment type. To summarize possible distributions and range of effects, in RCTs complete response was 44% (95% Confidence Interval (CI), 40% to 49%) in 28 intensive therapy studies [15,17–21,25,26,28,29,31,34–39,41–45,47–51,53], 18% (95% CI, 13% to 25%) in one low dose study [24], and 12% (95%

CI, 4% to 23%) in five best supportive care studies [16,24,27,30,32]. One-year survival was 36% (95% CI, 30% to 43%) in nine intensive therapy studies [15,17,18,28,29,34,38,49,53], 11% (95% CI, 6% to 18%) in one low dose study [46], and 17% (95% CI, 13% to 22%) in three best supportive care studies [16,27,30]. Finally, 30-day mortality was 19% (95% CI, 16% to 22%) in 20 intensive therapy studies [15,17,18,20,21,25,28,29,31,35,36, 38,41–43,45,47–50], and 14% (95% CI, 12% to 17%) in three best supportive care studies [16,27,32].

In the NRS, complete response was 45% (95% CI, 41% to 49%) in 25 intensive therapy studies [3,54–59,61–70,72,75,76,78–82], 24% (95% CI, 8% to 44%) in five low dose studies [54,65,66,78,80], 17% (95% CI, 12% to 24%) in three hypomethylating agent studies [55,56,74,77], and 1% (95% CI, 0% to 3%) in four best supportive care studies [3,55,56,61,65]. One-year survival was 37% (95% CI, 26% to 49%) in six intensive therapy studies [55–58,69,75], 35% (95% CI, 18% to 54%) in three hypomethylating agent studies [55,56,74,77], and 17% (95% CI, 12% to 24%) in two best supportive care studies [55,56,73]. Finally, 30-day mortality was 17% (95% CI, 12% to 22%) in 12 intensive therapy studies [3,55–58,64,66,70,75,78,79,81], 19% (95% CI, 8% to 36%) in one low dose study [78], 6% (95% CI, 1% to 13%) in three hypomethylating agent studies [55,56,74,77], and 34% (95% CI, 32% to 36%) in three best supportive care studies [3,55,56,64].

Beyond 1 year, survival decreased rapidly, and at 3 years, the survival was 16% (12–20%) with intensive therapy, 12% (5–21%) with low-dose therapy, 11% (7–15%) with hypomethylating agents, and 3% (1–6%) with best supportive care, highlighting a modest but real effect of active therapeutic choices.

Overall, the results were concordant between RCTs and NRSs.

Outcome data by ECOG PS was reported in 31 studies, by cytogenetics in 28 studies, by AML type in 22 studies, and by Charlson comorbidity index in 3 studies. Appendix Table 6 presents available data by risk category. Few patients belonged to the favorable cytogenetics subgroup. On forest plot analysis their outcomes did not differ significantly from the intermediate cytogenetics subgroup, so the results were grouped into favorable/intermediate vs poor. Pooling of data was not done by comorbidity index because a large number of missing not at random data led to biased estimates. One-year survival for patients treated with intensive chemotherapy with ECOG 0 to 1 was 38% (30–45%) compared to 28% (22–34%) in patients with ECOG 2+. Among patients treated with hypomethylating agents, one-year survival was 44% (35–54%) for patients with ECOG 0 to 1 and 47% (35–58%) in patients with ECOG 2+. Among patients treated with best supportive care, the one-year survival was 24% (20–28%) for patients with ECOG 0 to 1 and 8% (4–12%) among patients with ECOG 2+.

Similarly, one-year survival for patients treated with intensive chemotherapy with favorable or intermediate cytogenetics was 40% (36–45%) compared to 19% (13–25%) in patients with unfavorable cytogenetics. Among patients treated with hypomethylating agents, one-year survival was 60% (46–72%) for patients with favorable or intermediate cytogenetics and 27% (15–42%) in patients with unfavorable cytogenetics. Among patients treated with

best supportive care, the one-year survival was 23% (18–28%) for patients with favorable or intermediate cytogenetics and 12% (6–19%) among patients with unfavorable cytogenetics.

Finally, one-year survival for patients treated with intensive chemotherapy with de novo AML was 39% (31–48%) compared to 24% (10–42%) in patients with secondary AML. Among patients treated with hypomethylating agents, one-year survival was 45% (36–54%) for patients with de novo AML and 46% (35–58%) in patients with secondary AML. Among patients treated with best supportive care, the one-year survival was 19% (14–24%) for patients with de novo AML and 19% (14–24%) among patients with secondary AML.

We conducted a clinical review of the intensive regimens heterogeneity to assess whether a clear subgroup emerged (e.g. 3-drugs regimens vs 3 + 7, or addition of targeted therapies to 3+ 7). No relevant pattern was found.

4. Discussion

With data from 13,381 patients, this systematic review reports the largest cohort of older patients with AML to date and contains data from studies from multiple countries, including investigator-provided supplemental data. Moreover, we were able to evaluate subgroups by prognostic factors such as ECOG performance scores and cytogenetics, which are not available in large population registries such as SEER.

Although our findings appear to suggest that two therapeutic strategies (intensive treatment and hypomethylating agents) appear to produce markedly better survival than the others (low-dose chemotherapy and best supportive care), this result should be interpreted with caution, as it is an analysis based on parallel studies, without general adjustment for prognostic factors. Most studies had an incomplete reporting of cytogenetics, ECOG PS, and comorbidity, with only one study reporting all 3 predictors. Therefore, our analysis is best understood as the most comprehensive assessment of available body of knowledge on management and what can be achieved in the treatment studies of AML. Here we provide benchmarks for treatment efficacy and effectiveness that may be used for the future development of clinical trials. Of note, many of the studies were of limited size, therefore this analysis provides a strong quantitative improvement in the assessment of evidence.

We found after a systematic review that as of end of 2016, there were 38 RCTs and 30 NRS that enrolled 13,381 patients with available data specific to patients 70 years and older. To our surprise, even though a large number of intensive therapies were compared against each other, and low dose chemotherapies were compared against BSC, no eligible RCT compared intensive chemotherapy with hypomethylating agents despite the fact that latter two are widely used in practice. (One ineligible RCT, widely quoted to support the efficacy of hypomethylating agents in patients aged 65 and above, did include a mixed control group among which some patients did receive intensive chemotherapy. No subgroup data could be obtained to assess its impact in patients 70 and older [83]). Our review suggests that based on current evidence, such a study would be reasonable to conduct, with or without the addition of modern targeted or immune therapies, or substitution of 3 + 7 with regimens

such as CPX-351. As science progresses and better therapies become available, our analysis can be updated, and potentially further subgroups could be defined and analyzed.

The main limitation of our systematic review is reporting bias. Despite identifying 158 publications with a significant number of older patients, only 68 studies were able to provide outcome data on the older adult cohort. Among these, only 13% (5/38) of RCTs and 27% (8/30) of NRS exclusively enrolled patients over the age of 70. Additionally, many studies did not report all outcomes of interest. Extensive efforts were made to contact all authors and collaborative groups to acquire additional outcome and subgroup information. Even though we were unable to obtain data from every potentially eligible study, this systematic review is nevertheless the largest, most comprehensive review of newly diagnosed older patients with AML to date. A reassuring feature of our review is the overall concordance of results from RCTs (testing efficacy), and NRS (testing effectiveness), although the confidence intervals around certain outcomes are broad. Another potential limitation is that to provide power to our analyses we classified treatments into four subgroups. Although for most studies the classification is obvious, some readers may have classified some studies in another category. Our approach was rigorous and we were careful to establish clear criteria for eligibility and classification. A review of our forest plot outcome data did not identify systematic outliers among these borderline studies within our four categories. As any systematic review/meta-analytic approach, we had to define treatment and disease/patient categories that were broad enough to summarize a large number of studies. We had for example to leave out molecular classification data given the period covered by our review. We plan to update the study results as more publications become available with widely accepted molecular classifications, such as the European Leukemia Net classification [84]. We also hope that the push for inclusion of more comorbidity data in clinical trials and databases will add to that part of the information. Recent studies with targeted therapies have raised hopes for some subgroups of AML patients. The numbers of patients 70 and older enrolled in these studies is still very low, and they have only recently been published in full articles [85,86], a prerequisite for our analysis. Our study has been designed to be able to incorporate these new data in additional treatment categories, if need arise, as it is periodically updated.

Our data are of importance to clinicians and patients who now have the best possible assessment of benefits and harms of all current treatment modalities. Although we could not provide a definite answer about which treatment is best, our systematic review provides a platform for informed choices that patient and physician can rely on for shared decision making. Our systematic review provides a strong rationale for randomized comparisons of hypomethylating agents versus intensive chemotherapy based strategies for the treatment of AML patients above the age of 70. In addition, our data can be entered into a formal decision analysis model to integrate the adjusting prognostic variables into the comparison of the 4 types of treatments, with validated sensitivity analyses. This could provide a practical instrument on the basis of which to power future research questions. Periodic assessment of the totality of evidence is crucial to inform and prioritize future clinical research, and the two-step approach we propose (systematic review and model) can easily integrate future evidence.

Wider integration of the assessment of comorbidity is necessary as well to enhance the external validity of these trials. A model such as the one used by the German CLL group could be used (Cumulative Illness Rating Score-Geriatric <6 or > 6) [87] Nevertheless, given the still dismal 5-year survival of these older AML patients, new therapeutic strategies are needed. Broader integration of comorbidity and a geriatric assessment might also help identify in the future a subgroup of patients who may be candidates for bone marrow transplant, which still remains the most effective strategy.

In conclusion, this comprehensive, very large, systematic review of AML patients above the age of 70 identified more favorable outcomes for patients treated with intensive chemotherapy and hypomethylating agents than with low-dose chemotherapy and best supportive care, with the caveat that these results are overall unadjusted for prognostic variables.

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Appendix A. Appendix Methods

Appendix Table 1

Search strategy.

PubMed Observational Studies Search:

Keywords & Terms:

Limits:

Aml

acute myeloid leukemia

CER Observational Studies search strategy

aml OR acute myeloid leukemia

((elderly) AND ((aml OR acute myeloid leukemia)))

((elderly) AND ((aml OR acute myeloid leukemia))) AND CER Observational Studies search strategy

PubMed Randomized Control Trial Search

Keywords & Terms:

Limits:

Aml

acute myeloid leukemia

Cochrane Collaboration Highly Sensitive Search Strategy

aml OR acute myeloid leukemia
 ((elderly) AND ((aml OR acute myeloid leukemia)))
 ((elderly) AND ((aml OR acute myeloid leukemia))) AND Cochrane Collaboration Highly Sensitive Search Strategy
 Cochrane EBM Database Observational Studies Search
 Keywords & Terms:
 Limits:
 elderly.mp.
 acute myeloid leukemia.mp.
 aml.mp.
 aml.mp. OR acute myeloid leukemia.mp.
 Elderly.mp. AND (aml.mp. OR acute myeloid leukemia.mp.)
 SIGN Observational Search Strategy OVID
 Elderly.mp. AND (aml.mp. OR acute myeloid leukemia.mp.) AND SIGN Observational Search Strategy OVID
 Cochrane EBM Database Randomized Control Trial Search
 Keywords & Terms:
 Limits
 elderly.mp.
 acute myeloid leukemia.mp.
 aml.mp.
 aml.mp. OR acute myeloid leukemia.mp.
 Elderly.mp. AND (aml.mp. OR acute myeloid leukemia.mp.)
 Cochrane Highly Sensitive Search Strategy for identifying randomized trials OVID
 Elderly.mp. AND (aml.mp. OR acute myeloid leukemia.mp.) AND Cochrane Highly Sensitive Search Strategy for
 identifying randomized trials OVID

Appendix Table 2

Characteristics of included randomized controlled trials.

Study	Treatment Type	Induction regimen	Location (Group)	Multicenter	Enrollment period	Total number enrolled	Median age (range) in study	Total number of patient over age of 70	Outcomes with available data	Data available
Amadori 2005	Intensive	MICE ± GCSF	Europe (EORTC)	Yes	1995–2001	722	68 (61–80)	296	CR, OR, survival (1-yr, 2-yr, 3-yr, 5-yr), mortality (30-day, 60-day)	ECOG Cytotoxicity AM
Amadori 2013	Intensive	MICE ± GO	Europe (EORTC)	Yes	2002–2007	472	67 (60–75)	167	CR, OR, survival (1-yr, 2-yr, 3-yr, 5-yr), mortality (30-day, 60-day)	ECOG Cytotoxicity AM

Study	Treatment Type	Induction regimen	Location (Group)	Multicenter	Enrollment period	Total number enrolled	Median age (range) in study	Total number of patient over age of 70	Outcomes with available data	Data available
Amadori 2016	BSC	BSC ± GO	Europe (EORTC)	Yes	2004–2013	237	77 (62–88)	228	CR, OR, survival (1-yr, 2-yr, 3-yr, 5-yr), mortality (30-day, 60-day)	ECOG Cytotoxicity AM
Anderson 2002	Intensive	ME or AD	United States (SWOG)	Yes	1995–1998	328	[56–86]	132	CR, OR, survival (1-yr, 2-yr, 3-yr, 5-yr), mortality (30-day, 60-day)	ECOG Cytotoxicity AM
Archimbaud 1999	Intensive	Ara-C + ETO + (IDA or MTX)	Europe	Yes	1993–1996	160	69 (60–83)	69	CR	–
Baer 2002	Intensive	ADE ± PSC-833	United States (NCI - CLGB)	Yes	1998–1999	120	70 (60–84)	66	CR, OR, mortality (30-day, 60-day)	ECOG Cytotoxicity AM
Brunnberg 2012	Intensive	DNR or Ara-C + GO	Germany	Yes	2005–2009	119	[60–83]	49	CR, OR, mortality (30-day, 60-day)	ECOG Cytotoxicity AM
Burnett 2007	Low Dose	LD Ara-C + ATRA	United Kingdom	Yes	1998–2003	103	N/A	81	survival (2-yr, 3-yr, 5-yr)	–
	BSC	HU ± ATRA				99		77	survival (2-yr)	–
Burnett 2012	Intensive	DNR+ Ara-C or CLRFB ± GO	United Kingdom and Denmark	Yes	2006–2010	1115	67 [51–84]	342	survival (2-yr)	–
Burnett 2013	Low Dose	LD Ara-C	United Kingdom,	Yes	2006–2011	206	74 (54–90)	164	CR, survival (2-yr)	–
	BSC	CLRFB	Denmark, and Australia			200	74 (51–87)	166	CR, survival (2-yr)	–
Cripe 2010	Intensive	Ara-C + DNR ± ZQS	United States (NCI-ECOG)	Yes	2002–2005	449	69 IQR [65–73]	203	CR, survival (2-yr), mortality (30-day, 60-day)	ECOG Cytotoxicity AM
Dombret 1995	Intensive	Ara-C + DNR ± GCSF	Europe (AML-CSG)	Yes	1990–1992	173	70 (64–83)	88	CR	–
Erba 2014	BSC	TPF	United States (NCI-SWOG)	Yes	2004–2006	331	78 (70–94)	331	CR, OR, survival (1-yr, 2-yr, 3-yr, 5-yr), mortality	ECOG Cytotoxicity AM

Study	Treatment Type	Induction regimen	Location (Group)	Multicenter	Enrollment period	Total number enrolled	Median age (range) in study	Total number of patient over age of 70	Outcomes with available data	Data available
Godwin 1998	Intensive	Ara-C + DNR ± G-CSF	United States (NCI-SWOG)	Yes	1992–1994	211	68 (56–88)	74	(30-day, 60-day) CR, survival (1-yr, 2-yr, 3-yr, 5-yr), mortality (30-day, 60-day)	ECOG Cyt
Goldstone 2001	Intensive	DAT or ADE or MAC	Multinational (MRC)	Yes	1990–1998	1314	66 (44–91)	127	CR, OR, survival (1-yr, 2-yr, 3-yr, 5-yr), mortality (30-day, 60-day)	ECOG Cyt
Harousseau 2009	BSC	BSC or TPF	Multinational (FIGHT AML 301)	Yes	2004–2007	457	76 (69–90)	457	CR, survival (1-yr)	ECOG Cyt
Kahn 1984	Intensive	Ara-C + DNR + (TG full or att. dose)	United States (ECOG)	Yes	1981–1982	40	N/A	40	CR, mortality (30-day, 60-day)	–
Kantarjian 2012a	Low Dose	LD Ara-C	Multinational	Yes	2006–2009	215	73 (64–91)	173	survival (3-yr)	–
	HMA	DCTB				242	73 (64–89)	171	survival (3-yr)	–
Kantarjian 2012b	BSC	Sapacitabine	United State	Yes	2007–2009	105*(60 randomized)	77 (70–91)	60	CR, mortality (30-day, 60-day)	–
Karp 2012	Intensive	TPF + ETO	United States (NCI)	Yes	2008–2009	84* (42 randomized)	76 (70–90)	42	CR, survival (1-yr)	ECOG
Krug 2016	Intensive	HAM-HAM or TAD-HAM	Germany	Yes	1999–2011	3375	61 (16–86)	631	CR, OR, survival (5-yr), mortality (30-day, 60-day)	–
Lancet 2014	Intensive	Ara-C + DNR or CPX-351	United States and Canada	Yes	2008–2009	126	68 (60–77)	49	CR, OR, survival (2-yr), mortality (30-day, 60-day)	ECOG Cyt AM
Lowenberg 1997	Intensive	Ara-C + DNR ± G-CSF	Europe (EORTC and HOVON)	Yes	1990–1994	318	68 (61–88)	124	CR	–
Lowenberg 1998	Intensive	Ara-C + (DNR or MTX)	Europe (EORTC-LCG, HOVON)	Yes	1986–1993	539	68 (60–88)	199	CR, OR, survival (1-yr, 2-yr, 3-yr, 5-yr), mortality (30-day, 60-day)	ECOG Cyt

Study	Treatment Type	Induction regimen	Location (Group)	Multicenter	Enrollment period	Total number enrolled	Median age (range) in study	Total number of patient over age of 70	Outcomes with available data	Data available
Lowenberg 2009	Intensive	Ara-C + DNR	Europe (HOVON, AMLSG, and SAKK)	Yes	2000–2006	813	67 (60–83)	213	CR	–
Muller-Tidow 2016	Intensive	Ara-C + DNR ± AZA	Germany	Yes	2010–2011	214	70	57	survival (2-yr)	–
Oberg 2002	Intensive	Ara-C + TG + (DNR or ACR)	Sweden	Yes	1984–1988	90	72 (60–89)	48	CR, mortality (30-day)	–
Pigneux 2007	Intensive	Ara-C + IDA ± LOM	France (BGMT)	Yes	1995–2001	364	60–84	155	CR, OR, survival (5-yr), mortality (30-day, 60-day)	ECOG Cyt
Pigneux 2010	Intensive	Ara-C + IDA ± LOM	France (GOELAMS)	Yes	1995–2005	847	60–86	371	CR, OR, survival (2-yr), mortality (30-day, 60-day)	ECOG Cyt
Rowe 2004	Intensive	Ara-C+ (DNR or MTX or IDA)	United States (ECOG)	Yes	1993–1997	348	56–86	120	CR	–
Ruutu 2004	Intensive	Ara-C + IDA + (ETI or TAI)	Finland (Finnish Leukemia Group)	Yes	N/A	92	72	43 (65–84)	CR, OR, survival (3-yr, 5-yr), mortality (30-day, 60-day)	ECOG Cyt AM Con
Sekeres 2013	Low Dose	Ara-C ± Lintuzumab	International	Yes	2007–2010	211	70 (60–90)	119	survival (1-yr)	–
Serve 2013	Intensive	Ara-C + DNR ± sorafenib	Germany	Yes	2006–2008	197	68 (61–80)	81	CR, OR, mortality (30-day, 60-day)	ECOG Cyt AM
Stone 1995	Intensive	Ara-C + DNR ± GCSF	United States (CALGB)	Yes	1990–1993	388	69	172	CR, OR, survival (5-yr), mortality (30-day, 60-day)	ECOG
Stone 2015	Intensive	Ara-C + (DNR or AMF)	International	Yes	2008–2010	433	64 (19–84)	103	CR, OR, survival (1-yr), mortality (30-day, 60-day)	ECOG Cyt AM
Tassara 2014	Intensive	Ara-C + IDA + (ATRA or VPA)	Germany	Yes	2004–2006	186	68	69	CR, OR, survival (5-yr), mortality (30-day, 60-day)	ECOG Cyt AM

Study	Treatment Type	Induction regimen	Location (Group)	Multicenter	Enrollment period	Total number enrolled	Median age (range) in study	Total number of patient over age of 70	Outcomes with available data	Data available for subgroups
Van Der Holt 2005	Intensive	Ara-C + DNR ± PSC-833	International	Yes	1997–1999	428	67 (58–85)	125	CR	–
Wakita 2012	Intensive	BHAC + DNR	Japan (JALSG)	Yes	2000–2005	245	65–80	137	CR, survival (1-yr, 2-yr, 3-yr, 5-yr)	–

HAM, high-dose cytarabine and mitoxantrone; TAD, thioguanine, cytarabine and daunorubicin; Ara—C, cytarabine; DNR, daunorubicin; TG, 6-thioguanine; ETO, etoposide; ZQS, TPF, Tipifarnib; DCTB, decitabine; ACR, aclarubicin; LOM, lomustine, ETI, etoposide, thioguanine, idarubicin; TAI, thioguanine, cytarabine, idarubicin; AMF, amonafide L-malate; VPA, valproic acid; ATRA, all-trans retinoic acid; BHAC, behenoyl cytarabine; MTX mitoxantrone.

The median age and range are provided as reported by each included publication. For analysis purposed, data were only collected for patients over 70 years of age

Appendix Table 3

Characteristics of included non-randomized studies.

Study	Treatment Type	Induction regimen	Location (Group)	Multicenter	Enrollment period	Total number enrolled	Median age (range) in study	Total number of patient over age of 70	Outcomes with available data	Data available for subgroups
Astrom 2000	Intensive	Ara-C+ (IDA or MTX or TG or ETO)	Sweden	Yes	Retrospective 1987–1992	120	69.5	22	CR	–
	Low Dose	LD Ara-C+ (TG or/and ETO)	Sweden	Yes	Retrospective 1987–1992	60	–	52	CR	–
	BSC	BSC	Sweden	Yes	Retrospective 1987–1992	34	–	29	–	–
Bertoli 2013/ Bories 2014	Intensive	various	France	Yes	2000–2010	–	–	122	CR, OR, survival (1-yr, 2-yr, 3-yr, 5-yr), mortality (30-day, 60-day)	ECOG PS, Cytogenetic AML type, Comorbidity
	HMA	AZA	France	Yes	2000–2010	–	–	106	CR, OR, survival (1-yr, 2-yr, 3-yr, 5-yr), mortality (30-day, 60-day)	ECOG PS, Cytogenetic AML type, Comorbidity
	BSC	BSC	France	Yes	2000–2010	–	–	115	CR, OR, survival (1-yr), mortality (30-day, 60-day)	ECOG PS, Cytogenetic AML type

Study	Treatment Type	Induction regimen	Location (Group)	Multicenter	Enrollment period	Total number enrolled	Median age (range) in study	Total number of patient over age of 70	Outcomes with available data	Data available for subgroups
Chauncey 2010 (S0112)	Intensive	Ara-C + DNR	United States (SWOG)	Yes	2001–2003	60	68 (56–85)	27	CR, OR, survival (1-yr, 2-yr, 3-yr, 5-yr), mortality (30-day, 60-day)	ECOG PS, AML type
Chauncey 2010 (S0301)	Intensive	Ara-C + DNR + cyclosporine	United States (SWOG)	Yes	2003–2006	64	56–81	25	CR, OR, survival (1-yr, 2-yr, 3-yr, 5-yr), mortality (30-day, 60-day)	ECOG PS, AML type
Etienne 2007/Vey 2004	Intensive	various	France	No	1990–2004	–	–	147	CR, survival (1-yr, 2-yr, 3-yr, 5-yr), mortality (30-day, 60-day)	ECOG PS, Comorbidity
Farag 2006	Intensive	various	United States (CALGB)	Yes	1984–1999	635	68 (60–86)	262	CR, survival (5-yr)	–
Fattoum 2015	Intensive	various	France	No	Retrospective 2000–2014	499	60–83	95	OR, survival (3-yr)	Cytogenetic
	Low Dose	LD-Ara-C	France	No	Retrospective 2000–2014			60	OR, survival (3-yr)	Cytogenetic
	HMA	AZA or DAC	France	No	Retrospective 2000–2014			34	OR, survival (3-yr)	Cytogenetic
	BSC	BSC	France	No	Retrospective 2007–2014			107	OR, survival (3-yr)	Cytogenetic
Ferrara 1998	Intensive	Ara-C+ (DNR or IDA)	Italy	Yes	1987–1996	22	80	22	CR	–
	BSC	BSC	Italy	Yes	1987–1996	41	80	41	CR	–
Gardin 2013	Intensive	DNR or IDA	France (ALFA)	Yes	1999–2006	727	67	281	CR, survival (5-yr)	–
Gupta 2007	Intensive	Ara-C + DNR	Canada	No	1998–2005	291	68	120	CR, survival (3-yr)	–
Harb 2009	Intensive	Various	United States	No	1991–2007	59	84	59	CR, mortality (30-day)	–
	BSC	BSC	United States	No	1991–2007	33	83	33	Mortality (30-day)	–
Heiblig 2016	Intensive	Various	France	No	2000–2014	95	72 (70–79)	95	CR, survival (3-yr)	Cytogenetic

Study	Treatment Type	Induction regimen	Location (Group)	Multicenter	Enrollment period	Total number enrolled	Median age (range) in study	Total number of patient over age of 70	Outcomes with available data	Data available for subgroups
	Low Dose	LD Ara-C or HMA	France	No	2000–2014	100	76 (70–86)	100	CR, survival (3-yr)	Cytogenetic
	BSC	BSC	France	No	2000–2014	107	78 (70–93)	107	CR, survival (3-yr)	Cytogenetic
Iwakiri 2002	Intensive	Ara-C + DNR + MCP	Japan	No	1989–1999	53	74	53	CR, mortality (30-day)	–
Johnsen 1989	Low Dose	LD Ara-C	Japan	No	1989–1999	17	(60–88)	24	CR, OR	–
	Intensive	Ara-C + DNR	Denmark	No	Retrospective 1976–1986	264	59 (7–88)	39	CR	–
Juliusson 2009	Intensive	Various	Sweden (Swedish Acute Leukemia Registry)	Yes	Retrospective 1997–2005	1715	72	1129	CR, mortality (30-day, 60-day)	ECOG PS, Cytogenetic AML type
	BSC	BSC	Sweden	Yes	Retrospective 1997–2005	1044		1619	CR, mortality (30-day, 60-day)	ECOG PS, Cytogenetic AML type
Kahl 2016	Intensive	Ara-C + MTX	Germany	Yes	1998–2005	618	72	97	CR	–
Kantarjian 2006	Intensive	Various	United States	No	Retrospective 1980–2004	998	71 (65–89)	626	CR, survival (1-yr), mortality (60-day)	–
Kantarjian 2010a	Intensive	Various	United States	No	1990–2008	446	74 (70–88)	446	CR, OR, survival (2-yr, 3-yr), mortality (30-day, 60-day)	ECOG PS, Cytogenetic
Kantarjian 2010b	BSC	Clorafabine	United States	Yes	–	112	71 (60–88)	69	OR	–
Knipp 2007	Intensive	Ara-C + DNR + (IDA or TG or ETO)	Germany	No	1991–2004	160	66 (60–77)	84	CR	–
Latagliata 2002	BSC	BSC	Italy	Yes	Retrospective 1989–1998	60	72 (60–90)	54	Survival (1-yr)	–
Lubbert 2012	HMA	DAC	Europe	Yes	2003–2007	227	72 (56–86)	87	CR, survival (1-yr), mortality (30-day, 60-day)	ECOG PS, Cytogenetic AML type
Mori 2006	Intensive	BHAC +DNR + 6MP	Japan (JELLSG)	Yes	1997–2001	65	79	65	CR, survival (1-yr, 2-yr, 3-yr, 5-yr), mortality (30-day)	ECOG PS, Cytogenetic AML type

Study	Treatment Type	Induction regimen	Location (Group)	Multicenter	Enrollment period	Total number enrolled	Median age (range) in study	Total number of patient over age of 70	Outcomes with available data	Data available for subgroups
Nagura 1999	Intensive	Various	Japan	Yes	1990–1995	159	69	55	CR	–
Nand 2013	HMA	HU + AZA + GO	United States	Yes	N/A	142	57–87	98	CR, OR, survival (1-yr, 2-yr, 3-yr, 5-yr), mortality (30-day, 60-day)	ECOG PS, AML type
Oshima 2012	Intensive	Various	Japan	Yes	Retrospective 1994–2004	45	76 (70–97)	45	CR, survival (3-yr), mortality (30-day, 60-day)	ECOG PS, Cytogenetic AML type
	Low Dose	Various	Japan	Yes	Retrospective 1994–2004	36		36	CR, survival (3-yr), mortality (30-day, 60-day)	ECOG PS, Cytogenetic AML type
Ross 2015	Intensive	Various	United States	No	Retrospective 2000–2013	62	73 (70–87)	62	CR, OR, mortality (30-day, 60-day)	Cytogenetic AML type
Takahashi 2016	Low Dose	CLDA	United States	No	Retrospective 2002–2012	95	68 (60–80)	38	CR	–
	Intensive	IA	United States	No	Retrospective 2002–2012	95	67 (60–85)	38	CR	–
Walters 1987	Intensive	Ara-C + various	United States	No	Retrospective 1973–1984	78	70–86	78	CR, mortality (30-day)	Cytogenetic AML type
Xu 2014	Intensive	Ara-C + various	China	No	retrospective 2006–2013	129		39	CR	–
	BSC	BSC	China	No	retrospective 2006–2013	23	68 (60–94)	20	–	–

m-AMSA, Amsacrine; AZA, azacytidine; BHAC,; BSC, Best Supportive Care; CLDA, clorafabine+LD Ara—C; DAC, 5-aza-2'-deoxycytidine (decitabine); DNR, daunorubicin; ETO, etoposide; GO, gemtuzumab ozogamicin; HMA, hypomethylating agents; HU, hydroxyurea; IA, Ara-C + IDA; IDA, idarubicin; LD, low-dose; MCP, 6-mercaptopurine; MTX, methotrexate; TG, thioguanine.

Appendix Table 4

Risk of bias in included randomized controlled trials.

Study	Selection bias - randomization	Selection bias – allocation concealment	Performance bias	Detection bias ¹	Attrition bias	Reporting bias	Other bias
Amadori 2005	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Amadori 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk

Study	Selection bias - randomization	Selection bias – allocation concealment	Performance bias	Detection bias ¹	Attrition bias	Reporting bias	Other bias
Amadori 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Anderson 2002	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Archimbaud 1999	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Baer 2002	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Brunnberg 2012	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Burnett 2007	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Burnett 2012	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Burnett 2013	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Cripe 2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Dombret 1995	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Erba 2014	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Godwin 1998	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Goldstone 2001	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Harousseau 2009	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Kahn 1984	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Kantarjian 2012a	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	High risk
Kantarjian 2012b	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Karp 2012	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	High risk
Krug 2016	Low risk	Unclear risk	Low risk	Low risk	Low risk	High risk	Unclear risk

Appendix Table 5

Risk of bias in included non-randomized studies.

Study	Study Design	Representative cohort	Ascertainment of exposure	Outcomes not present at start	Outcome assessment	Adequate follow-up time	Adequate subject followed up (>80%)
Astrom 2000	Retrospective	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Study	Study Design	Representative cohort	Ascertainment of exposure	Outcomes not present at start	Outcome assessment	Adequate follow-up time	Adequate subject followed up (>80%)
Bertoli 2013/ Bories 2014	Retrospective	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Chauncey 2010 (S0112)	Prospective	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Chauncey 2010 (S0301)	Prospective	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Etienne 2007/Vey 2004	Retrospective	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Farag 2006	Retrospective	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Fattoum 2015	Retrospective	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ferrara 1998	Retrospective	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Gardin 2013	Retrospective	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Gupta 2007	Retrospective	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Harb 2009	Retrospective	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Heiblig 2016	Retrospective	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Iwakiri 2002	Retrospective	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Johnsen 1989	Retrospective	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Juliusson 2009	Retrospective	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kahl 2016	Prospective	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kantarjian 2006	Retrospective	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kantarjian 2010a	Retrospective	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kantarjian 2010b	Prospective	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Knipp 2007	Retrospective	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Latagliata 2002	Retrospective	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
Lubbert 2012	Prospective	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Mori 2006	Prospective	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Nagura 1999	Retrospective	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk

Study	Study Design	Representative cohort	Ascertainment of exposure	Outcomes not present at start	Outcome assessment	Adequate follow-up time	Adequate subject followed up (>80%)
Nand 2013	Prospective	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Oshima 2012	Retrospective	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ross 2015	Retrospective	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Takahashi 2016	Retrospective	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Walters 1987	Retrospective	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Xu 2014	Retrospective	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk

Appendix Table 6

Proportion of patients with outcome by performance status, cytogenetics, AML type, and comorbidity score.

Subgroup/ Outcome	By ECOG PS				By Cytogenetics				By AML type	
	Number of studies (patients)	Proportion (95% CI)	Number of studies (patients)	Proportion (95% CI)	Number of studies (patients)	Proportion (95% CI)	Number of studies (patients)	Proportion (95% CI)	Number of studies (patients)	Proportion (95% CI)
	ECOG (0–1)		ECOG (2+)		Favorable + Intermediate		Unfavorable		De novo	
Intensive										
Complete response	18 (1844)	40% [32–48]	15 (761)	35% [29–40]	15 (1319)	51% [44–58]	15 (600)	30% [24–36]	10 (717)	43% [39–51]
Overall response	7(726)	50% [41–59]	5(231)	40% [31–49]	5 (405)	49% [37–62]	5(171)	41% [33–49]	2(343)	50% [39–55]
1-year survival	14 (1327)	38% [30–45]	11 (560)	28% [22–34]	9(846)	40% [36–45]	9 (417)	19% [13–25]	5(485)	39% [34–48]
2-year survival	17 (1771)	20% [17–24]	13 (688)	16% [11–22]	14(1253)	23% [19–27]	12(558)	6% [3–10]	10 (757)	23% [19–29]
3-year survival	11 (950)	15% [10–19]	9(344)	13% [8–19]	9 (630)	18% [12–24]	8 (226)	3% [0–7]	6(514)	15% [10–20]
5-year survival	14 (1231)	12% [7–18]	12 (453)	8% [4–13]	10(690)	12% [8–16]	9 (266)	1% [0–3]	7 (564)	8% [4–12]
30-day mortality	11 (952)	12% [10–14]	8 (328)	28% [20–36]	7(542)	16% [12–21]	7(210)	19% [13–24]	5 (485)	15% [10–20]
60-day mortality	12 (1198)	23% [19–26]	9(512)	40% [31–48]	8 (809)	27% [23–32]	8 (373)	31% [23–40]	5 (485)	24% [19–30]
Low Dose										
Complete response	0	–	0	–	1 (57)	12% [5–24]	1 (30)	13% [4–31]	0	–
Overall response	0	–	0	–	0	–	0	–	0	–
1-year survival	0	–	0	–	0	–	0	–	0	–
2-year survival	1 (18)	39% [17–64]	1 (18)	6% [0–27]	1 (22)	27% [11–50]	0	–	1 (19)	21% [10–32]

Subgroup/ Outcome	By ECOG PS				By Cytogenetics				By AML type	
	Number of studies (patients)	Proportion (95% CI)	Number of studies (patients)	Proportion (95% CI)	Number of studies (patients)	Proportion (95% CI)	Number of studies (patients)	Proportion (95% CI)	Number of studies (patients)	Pro (95% CI)
	ECOG (0–1)		ECOG (2+)		Favorable + Intermediate		Unfavorable		De novo	
3-year survival	0	–	0	–	2 (95)	22% [14–31]	2 (43)	4% (0–13)	0	–
5-year survival	0	–	0	–	0	–	0	–	0	–
30-day mortality	0	–	0	–	0	–	0	–	0	–
60-day mortality	0	–	0	–	0	–	0	–	0	–
Hypomethylating Agents										
Complete response	2(111)	16% [9–23]	2(73)	20% [12–31]	1 (57)	12% [5–24]	1 (45)	11%[4–24]	2 (127)	19% [27–27]
Overall response	1 (44)	36% [22–52]	1 (54)	35% [23–49]	0	–	0	–	1 (76)	38% [50–50]
1-year survival	2(111)	44% [35–54]	2(73)	47% [35–58]	1 (57)	60% [46–72]	1 (45)	27% [15–42]	2 (127)	45% [54–54]
2-year survival	2(111)	22% [15–31]	2(73)	20% [11–31]	1 (57)	37% [24–51]	1 (45)	13% [5–27]	2 (127)	20% [37–37]
3-year survival	3 (138)	10% [5–16]	2(73)	13% [6–22]	2 (69)	12% [5–22]	1 (45)	7%[1–18]	3 (142)	9% [9–9]
5-year survival	2(111)	4% [1–8]	1 (19)	0%(0–18)	2 (69)	4% (0–12)	1 (45)	0% (0–8)	3 (142)	0% [0–0]
30-day mortality	2(111)	2% (0–7)	2(73)	10% [4–19]	1 (57)	0% (0–6)	1 (45)	4% [1–15]	2 (127)	8% [8–8]
60-day mortality	2(111)	11% [6–18]	2(73)	24% [15–35]	1 (57)	4% (0–12)	1 (45)	22% [11–37]	2 (127)	18% [25–25]
Best supportive care										
Complete response	4(585)	7% [4–9]	3(225)	5% [2–10]	3(240)	4% (0–14)	4 (204)	1% (0–4)	3(361)	5% [5–5]
Overall response	2 (395)	12% [9–15]	2(162)	13% [8–19]	2(183)	14% [9–19]	2 (107)	4% [1–8]	2 (323)	12% [12–12]
1-year survival	2 (395)	24% [20–28]	2(162)	8% [4–12]	3(240)	23% [18–28]	2 (107)	12% [6–19]	3(361)	19% [24–24]
2-year survival	2 (395)	8% [6–11]	2(162)	3% [1–6]	2(183)	8%[5–13]	2 (107)	4% [1–8]	2 (323)	6% [6–6]
3-year survival	2 (395)	5% [3–7]	2(162)	1% (0–4)	2(183)	5%[2–9]	2 (107)	2% (0–6)	2 (323)	4% [4–4]
5-year survival	1(249)	2% [1–5]	1 (80)	0% (0–5)	1 (66)	0% (0–5)	1 (62)	2% (0–9)	1 (165)	2% [2–2]
30-day mortality	3 (420)	12% [8–16]	3 (177)	22% [6–43]	3(240)	14% [6–25]	3 (136)	31% [16–47]	3(361)	16% [22–22]
60-day mortality	3 (420)	26% [18–35]	3 (177)	47% [18–77]	3(240)	26% [12–42]	3 (136)	52% [29–75]	3(361)	32% [40–40]

Appendix Fig. 1.

Distribution of published studies/number of patients per year.

A) Comparisons reporting by performance status **C) Comparisons reporting by AML type** **B) Comparisons reporting by cytogenetics** **D) Comparisons reporting by comorbidities** **Appendix Fig. 2.**

Network diagram of available head to head comparisons by A) ECOG performance status, B) cytogenetics, C) AML type, and D) Comorbidity index. The nodes (circles) represent studies which assessed a particular treatment modality. The size of the node is proportional to number of studies. The lines between the nodes indicate studies which assessed more than one treatment modality.

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PRISMA flow diagram

Fig. 1.
Study selection flow diagram.

Fig. 2. Network diagram of available head to head comparisons in A) randomized controlled trials and B) non-randomized studies. The nodes (circles) represent studies which assessed a particular treatment modality. The size of the node is proportional to number of studies. The lines between the nodes indicate studies which assessed more than one treatment modality.

Table 1

Data sources for included studies:

Data source	Randomized controlled trials (RCT)	Non-randomized studies (NRS)	Overall
Individual patient data	9 studies (1596 patients)	5 studies (640 patients)	14 studies (2236 patients)
Query forms completed by original investigators	12 studies (1992 patients)	4 studies (2829 patients)	16 studies (4821 patients)
Published data only	17 studies (2831 patients)	21 studies (3493 patients)	38 studies (6324 patients)

Table 2

Summary of study characteristics.

	Randomized controlled trials	Non-randomized studies	Overall
Number of studies	38	30	68
Number of patients	6419	6962	13,381
Induction therapy type	41	46	878
Intensive	30	26	56
Low dose	4	6	10
Hypomethylating agents	1	4	5
Best supportive care	6	10	16
Years of publication			
1981–1990	1	2	3
1991–2000	6	3	9
2001–2010	14	14	28
2011–2016	16	11	27
Setting			
Multicenter	38	16	54
Single center	0	14	14
Cytogenetics extractable	18	10	28
Favorable/intermediate (#pts)	1225	1843	3068
Unfavorable(#pts)	667	968	1635
ECOG PS	21	10	31
0–1 (#pts)	2342	2004	4346
2+ (#pts)	824	1741	2565
Charlson	1	2	3
0 (#pts)	30	203	233
1+ (#pts)	13	111	124

Table 3

Proportion of patients with outcome by study and treatment type.

Subgroup/Outcome	Randomized controlled trials		Non-randomized studies		Overall	
	Number of studies (patients)	Proportion (95% CI)	Number of studies (patients)	Proportion (95% CI)	Number of studies (patients)	Proportion (95% CI)
Overall						
Complete response	33 (5399)	38% [30–46]	27(6461)	36% [30–42]	60 (11,860)	37% [32–42]
Overall response	18 (3269)	45% [37–54]	9 (1390)	41% [32–50]	27 (4659)	44% [37–51]
1-year survival	13(2412)	29%[22–37]	9 (1472)	31% [24–40]	22 (3884)	30% [25–35]
2-year survival	16 (3201)	17% [12–22]	7 (1036)	23% [17–29]	23 (4237)	18% [14–22]
3-year survival	12(2155)	8%[5–13]	11 (1835)	15% [12–19]	23 (3990)	11% [8–15]
5-year survival	15(2838)	8%[5–11]	8 (1133)	5% [3–8]	23 (3971)	7% [5–9]
30-day mortality	23 (3694)	18%[16–21]	14 (4300)	18% [14–22]	36(7994)	18% [16–20]
60-day mortality	22(3646)	29%[26–31]	11 (4638)	29% [25–34]	33(8284)	29%[26–31]
By treatment type Intensive						
Complete response	28(3993)	44% [40–49]	25 (4038)	45% [41–49]	53 (8031)	44% [41–47]
Overall response	16 (2710)	50% [46–54]	6 (777)	54% [47–62]	22 (3487)	51% [47–55]
1-year survival	9 (1277)	36% [30–43]	6 (1012)	37% [26–49]	15 (2289)	37% [31–42]
2-year survival	12(2154)	21% [16–26]	6 (832)	24% [17–32]	18(2986)	22% [18–26]
3-year survival	8 (1175)	12%[8–18]	10 (1187)	20% [14–26]	18 (2362)	16% [12–20]
5-year survival	12(2202)	9% [7–12]	7(929)	7% [4–11]	19 (3131)	8% [6–11]
30-day mortality	20(3075)	19%[16–22]	12 (2258)	17% [12–22]	32(5333)	18% [16–21]
60-day mortality	19(3027)	29% [26–32]	9 (2629)	26% [20–33]	28 (5656)	28%[25–31]
Low Dose						
Complete response	1 (164)	18%[13–25]	5(250)	24% [8–44]	6 (414)	22% [11–36]
Overall response	–	–	2 (84)	18% [10–27]	2 (84)	18% [10–27]
1-year survival	1 (119)	11%[6–18]	–	–	1 (119)	11% [6–18]
2-year survival	2(245)	11%[7–15]	–	–	2(245)	11% [7–15]
3-year survival	1(173)	5% [2–9]	3(196)	16% [11–21]	4(369)	12% [5–21]
5-year survival	–	–	–	–	–	–
30-day mortality	–	–	1 (36)	19% [8–36]	1 (36)	19% [8–36]

Subgroup/Outcome	Randomized controlled trials			Non-randomized studies			Overall	
	Number of studies (patients)	Proportion (95% CI)		Number of studies (patients)	Proportion (95% CI)		Number of studies (patients)	Proportion (95% CI)
60-day mortality	–	–	–	1 (36)	33% [19–51]	–	1 (36)	33% [19–51]
Hypomethylating Agents								
Complete response	–	–	–	3(291)	17% [12–24]	–	3(291)	17% [12–24]
Overall response	–	–	–	3 (238)	24% [13–38]	–	3 (238)	24% [13–38]
1-year survival	–	–	–	3(291)	35% [18–54]	–	3(291)	35% [18–54]
2-year survival	–	–	–	2(204)	22% [16–28]	–	2 (204)	22% [16–28]
3-year survival	1 (171)	10% [6–15]	–	3 (238)	12% [6–19]	–	4 (409)	11% [7–15]
5-year survival	–	–	–	2(204)	3% [1–6]	–	2 (204)	3% [1–6]
30-day mortality	–	–	–	3(239)	6% [1–13]	–	3 (239)	6% [1–13]
60-day mortality	–	–	–	3(239)	18% [11–25]	–	3 (239)	18% [11–25]
Best supportive care								
Complete response	5 (1242)	12% [4–23]	–	4(1882)	1% (0–3)	–	9(3124)	6% [2–11]
Overall response	2 (559)	12% [10–15]	–	3(291)	7% (0–35)	–	5 (850)	9% [2–21]
1-year survival	3 (1016)	17% [13–22]	–	2(169)	17% [12–24]	–	5 (1185)	17% [13–21]
2-year survival	4 (802)	6% [2–12]	–	–	–	–	4(802)	6% [2–12]
3-year survival	3 (636)	2% (0–5)	–	2(214)	6% [3–9]	–	5 (850)	3% [1–6]
5-year survival	3 (636)	1% (0–4)	–	–	–	–	3 (636)	1% (0–4)
30-day mortality	3 (619)	14% [12–17]	–	3 (1767)	34% [32–36]	–	6 (2386)	23% [14–34]
60-day mortality	3 (619)	28% [23–34]	–	2 (1734)	49% [46–51]	–	5 (2353)	36% [25–48]