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Research paper

Efficacy outcomes in the treatment of older or medically unfit patients with acute myeloid leukaemia: A systematic review and meta-analysis

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ABSTRACT

Older and medically unfit patients with acute myeloid leukaemia (AML) who are unsuitable for standard induction therapy have limited treatment options. A meta-analysis was performed with two objectives: 1) to describe outcomes for patients treated with hypomethylating agents, either decitabine or azacitidine, or low-dose cytarabine (LDAC) and 2) to describe the effect of age (< 75 vs ≥75) on the remission rates. Thirteen published multi-centre studies in 1822 patients were identified where patients were treated with hypomethylating agents or LDAC. A random effects meta-analysis was performed to provide a pooled estimate of efficacy for the following endpoints: complete remission (CR), overall response rate (CR + complete remission with incomplete white blood cell recovery [CRi]), relapse free survival (RFS), overall survival (OS), and 60-day mortality. For all endpoints apart from RFS, there was significant unexplained between-trial variability ($I^2 > 64\%$). The pooled estimates of average outcome across studies were 15% (95% CI: 12%–19%) for CR; 22% (95% CI: 18%–26%) for overall response rate; 8.8 months (95% CI: 7.7 m–10.0 m) for median RFS; 6.3 months (95% CI: 5.3 m–7.4 m) for median OS and 21% (95% CI: 18%–25%) for 60-day mortality. The odds of response were 1.85 times higher (95% CI: 1.3–2.7) among patients who were < 75 compared to those who were older.

1. Introduction

Acute myeloid leukaemia (AML) is a heterogeneous haematological malignancy characterized by abnormal proliferation of immature haematopoietic progenitor cells of the myeloid lineage. AML is an uncommon disease, accounting for less than 1.2% of all cancers. AML is recognized as a disease of older adults, with a median age at presentation of 68 years and advanced age being an adverse prognostic factor [1,2].

The general therapeutic strategy for AML patients has not changed substantially in over 40 years [3,4]. Therapy is based on initial assessment to determine whether a patient is a suitable candidate for intensive chemotherapy. The backbone of this intensive therapy is an anthracycline (daunorubicin or idarubicin) and cytarabine (cytosine arabinoside, Ara-C), which is associated with severe bone marrow and gastrointestinal toxicities. This standard induction therapy, known as 7 + 3, is particularly poorly tolerated by the older or unfit population and is associated with high treatment-related mortality rates with limited overall benefit. Therefore, there is no standard of care for such patients, in contrast with the "7 + 3" that has been established for younger AML patients for 45 years [5]. Age, general health status and the presence of organ dysfunctions or comorbidities are major factors contributing to treatment choice and chances of success. Older adults, especially at the age of 75 years or older, are more likely to have comorbidities that can limit treatment options, and in addition, the disease also tends to be more resistant to chemotherapy with more frequent unfavourable AML subtypes [1]. As a result, outcomes are generally worse than in younger patients. Low-dose cytarabine (LDAC) is an acceptable low-intensity therapeutic strategy for the treatment of this population and in a large prospective randomised study, has been shown to be superior to hydroxyurea [6]. Over the last several years, hypomethylating agents therapy with either decitabine or azacitidine, have also been increasingly used in older or unfit AML patients, and together with LDAC offer the main backbone treatment option for this population, either as single agents or in combination with targeted therapies such as the BCL2 inhibitor venetoclax or the sonic hedgehog

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pathway inhibitor glasdegib, both recently approved for first-line treatment of this population [7,8].

Yet, despite the extensive use of these agents, there is no consensus regarding the extent of efficacy and clinical benefit of hypomethylating agents and LDAC, with notable between-study variability observed for reported outcomes, presumably due to selection of patients with varying baseline characteristics which are known to affect outcome. Two large randomised studies [9,10] have compared hypomethylating agents to conventional care regimens, which included LDAC, in patient populations restricted to AML. In neither study was the primary analysis of overall survival statistically significant.

The importance of a comprehensive and methodical analysis of the outcomes of hypomethylating agents and LDAC is even more pronounced in light of the conditional approvals of new therapies such as the venetoclax combination therapy based on single-arm studies.

The purpose of this study is to quantify the expected outcomes with currently available therapies for older and unfit AML patients, hypomethylating agents or LDAC, to provide a benchmark of data that will be useful in the assessment of future agents particularly those studied in early phase trials.

2. Materials and methods

2.1. Study and data selection

In October 2017, Medline and Google were searched for completed trials of LDAC and the hypomethylating agents, decitabine or azacitidine, in older AML patients, unfit for standard induction therapy, using search terms (and their combinations) including:" AML", "acute myeloid leukemia", "older/elderly patients", "unfit (for standard therapy) patients", "not eligible for standard induction therapy", "hypomethylating agent/s", "azacitidine", decitabine", "low-dose cytarabine/Ara-C", "LDAC", between 2007-2017. Of these, trials were selected if performed in a population of patients not eligible for standard induction therapy, sometimes described as an older unfit population. In addition, only multicentre trials were included to reduce selection bias. Following the FDA approval of glasdegib in 2018, data from the LDAC control arm of the pivotal trial were also included. The meta-analysis only included data from LDAC, decitabine and azacitidine monotherapy arms and data from experimental arms such as clofarabine, vosaroxin, volasertib, vorinostat and valproic-acid containing regimens were excluded from the meta-analysis. One study [11] was presented only in abstract form, and only contained data for one endpoint, overall survival (OS), that used a definition consistent with other studies; relevant data were included to be as complete as possible. In one publication [12] the patient population consisted only of patients with blast counts of between 20 and 30%, originally classified as high-risk MDS but later re-classified as AML. This trial was not included as the population was not considered representative of a broader AML population. This search identified 16 cohorts from 13 multicentre studies, in 1822 patients (Table 1). The dose and schedule of the respective agents was generally consistent.

Some of the trials, [9,10], recruited a broader population of patients randomising between a hypomethylating agent or investigator choice of therapy: best-supportive care, intensive chemotherapy or LDAC. The choice of control therapy was declared prior to randomisation. For this meta-analysis, where possible and unless indicated otherwise, only data from patients who were pre-selected to receive LDAC prior to randomisation were included in order to provide representative outcomes for the intended population.

Four of the trials [6,13,17,18] included a small proportion of patients who met the definition of high-risk MDS, however, these represented at most 16% of the patients included per study in this analysis. Where data presentations excluded the MDS patients these were included in the pooled-analysis, otherwise the estimates from the entire population were included. In the only study [17] where response rate data were presented according to high-risk MDS patients, response rate amongst MDS patients was almost identical to the overall population. Therefore, the inclusion of a small number of MDS patients is not expected to have influenced the meta-analysis by any meaningful amount.

In three of the trials [6,11,16] all-trans retinoic acid (ATRA) was added as part of the regimen. In randomised comparisons [6,11], ATRA was concluded to have had no effect on response rate however in one of the same studies [11] there was an apparent effect of ATRA on overall survival. To maximise the amount of data available for the meta-analysis and the inconsistent evidence for an effect of ATRA we decided to include all data from regimens that additionally included ATRA.

Data were available to quantify the effect of age, using a cut-off of < 75 vs ≥ 75 years, from 3 treatment arms across 2 studies. This age cut-off is used for an unfitness definition in most prospective clinical studies. In one study [17], the response rates were compared for the proportion of patients with CR or CR with incomplete haematological recovery (CRi) and in the other study [16], rates were compared for partial response or better. Whilst subgroup analyses of OS were reported from many of the studies, only one study presented the effect of age ≥ 75 on OS within treatment arms. Given the effect of age on OS has been reported extensively elsewhere [1,22–26] the analyses in this study were limited to the effect of age ≥ 75 on the response rates.

2.2. Outcome measures

A pooled analysis was performed for CR, overall response rate (CR + CRi), median relapse free survival (RFS), median OS and 60-day mortality. Median OS was available for all studies. Data for all other endpoints were available for at least eight of the thirteen studies.

The definition of CR was consistently applied in all studies as bone marrow blasts $< 5\%$; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count $> 1.0 \times 10^9$/L (1,000/μL); platelet count $> 100 \times 10^9$/L (100,000/μL) [27]. Overall response includes patients with a CR and additionally those patients who met all CR criteria but only one of those requiring recovery of neutrophil and platelet counts (CRi). In one study [13], overall response also included patients with a best response of marrow CR (which do not requires recovery of either neutrophil or platelet).

Overall survival was consistently defined across all studies to include all deaths regardless of cause and whether they followed the addition of subsequent therapy. Median OS was pooled across studies. For three of the studies [6,13,17] median OS was not reported but could be estimated from the presented Kaplan-Meier (KM) curves. Early mortality data were captured by pooling 60-day mortality defined as the proportion of patients who died within 60 days of receiving therapy, if this outcome was not explicitly stated it was estimated from the KM curve.

There was more variability in the definition of RFS used between studies. In general, the end of response was defined as the earliest of relapse from response or death. In one study [9], any patients who was lost-to-follow-up (LTFU) were also included as an event at the time they were LTFU. In another study [19], responding patients who received additional therapy prior to relapse were censored. Some studies presented RFS amongst patients with a CR and in others this was based on patients with either a CR or CRi (Table 3). Nevertheless, given the consistency in outcomes between trials the pooled result is presented as a reference.

2.3. Statistical analyses

Sixteen separate cohorts were created from the thiteen studies included. For the two randomised trials comparing hypomethylating agents to LDAC, the results of the experimental and comparator arm were analysed separately. For the Dennis study [18], the two sequential, 51 patient control arms of LDAC were analysed separately. The contribution of each cohort was weighted down to 40 patients as 22

Table 1
Studies included in the meta-analysis.

Study (primary author, year)	Agent	Dose and schedule	N
Craddock 2017 [13]	Azacitidine	75 mg/m^2 5-2-2[1] every 4 weeks	129
Dombret 2015 [9]	Azacitidine	75 mg/m^2 7-days every 4 weeks	154
Passweg 2014 [14]	Azacitidine	100 mg/m^2 5-days every 4 weeks	45
Cashen 2010 [15]	Decitabine	20 mg/m^2 5-days every 4 weeks	55
Kantarjian 2012 [10]	Decitabine	20 mg/m^2 5-days every 4 weeks	242
Lubbert 2012 [16]	Decitabine	15 mg/m^2 t.i.d. 3-days every 6 weeks	227
Lubbert 2016 [11]	Decitabine	20 mg/m^2 5-days every 4 weeks	100[2]
Burnett 2007 [6]	LDAC	20 mg/m^2 b.i.d. 10-days every 4 to 6 weeks	102
Burnett 2013 [17]	LDAC	20 mg/m^2 b.i.d. 10-days every 6 weeks	206
Dennis 2015, Cohort1 [18]	LDAC	20 mg/m^2 b.i.d. 10-days every 4 to 6 weeks	40[3]
Dennis 2015, Cohort2 [18]	LDAC	20 mg/m^2 b.i.d. 10-days every 4 to 6 weeks	40[3]
Döhner 2014 [19]	LDAC	20 mg/m^2 b.i.d. 10-days every 4 weeks	45
Dombret 2015 [9]	LDAC	20 mg/m^2 b.i.d. 10-days every 4 weeks	158
Kantarjian 2012 [10]	LDAC	20 mg/m^2 10-days every 4 weeks	215
Kantarjian 2013 [20]	LDAC	20 mg/m^2 b.i.d. 10-days every 4 weeks	26
Glasdegib [8,21]	LDAC	20 mg/m^2 b.i.d. 10-days every 4 weeks	38

N: number of patients from included arms;[1] 75 mg/m^2 daily for 5 days, followed by 2 days of no treatment and then 2 more treatment days. [2] assuming patients randomised equally to each arm. [3] 51 patients were dosed in each cohort but 22 patients appear in both cohorts so N reduced to 40 for the meta-analysis.

patients were included in both control arms, leaving 80 distinct patients across both cohorts. For the Craddock study [13], data from the decitabine alone and decitabine + ATRA arms were combined prior to inclusion.

The results from each cohort were pooled using a random effects meta-analysis [28] due to the presence of excess between study variability in outcome for all endpoints with the exception of RFS. The results were summarised using a point estimate and 95% confidence interval for the average of the different outcomes between studies. The proportion of the total variability in outcome that was accounted for by excess between study variability was quantified using the I^2 statistic [29]. In addition to an overall pooled estimate, separate pooled estimates were provided for each treatment class using the seven hypomethylating agents and nine LDAC cohorts. To inform the relevance of the separate treatment class estimates, a fixed effect meta-analysis was performed combining the treatment effects of the two randomised studies comparing a hypomethylating agent to LDAC amongst the subset of patients pre-selected to receive LDAC.

For the CR, overall response rate and 60-day mortality endpoints, the ln(odds) of response was analysed using $\frac{1}{r} + \frac{1}{(n-r)}$ as the variance, where r and n represent the number of responders and number of patients respectively. Having pooled the ln(odds) of response, data were back transformed to give a pooled estimate of the percentage patients responding or dying within 60 days as appropriate. For OS and RFS, the ln(median) values were analysed using $\frac{1}{e}$ as the variance [30], where e represents the number of events observed (deaths/relapses as appropriate). Having pooled the ln(median) values, results were exponentiated to give a pooled estimate of the median. For OS, some studies did not report the number of deaths directly but these could be deduced from the width of the confidence for the hazard ratio. Likewise, for RFS the number of relapses was not always presented but an approximate number was derived from the width of the confidence interval for median RFS or from the number of steps on the KM curve. For 60-day mortality, rates were estimated from KM curves if they weren't presented separately.

The effect of age, 75 years or older, on overall response rate or partial response was reported in three cohorts of 631 patients across two studies [16,17] including patients randomised to the clofarabine arm. A fixed effect meta-analysis was performed on the ln(odds) of response to provide an overall estimate of the effect of age.

Funnel plots [31] are presented in the supplementary appendix that provide reassurance that the studies selected are not a biased sample.

3. Results

3.1. Study characteristics

A total of 1822 patients, from 16 cohorts across 13 studies were identified and available for pooling. Characteristics of these studies are presented in Table 2. Publication years of these studies ranged from 2007 to 2018. Efficacy outcomes are presented in Table 3.

3.2. Outcomes

The pooled CR rate was 15% (95% CI: 12%–19%, Fig. 1) with 64% of the variability in outcome representing excess between-study variation. Data are also presented according to class of agent however, a meta-analysis of the CR rate combining the two randomised trials comparing hypomethylating agents to LDAC did not reveal a statistically significant difference (p = 0.46). The pooled overall response rate was 22% (95% CI: 18%–26%, Fig. 1).

For the eleven cohorts where median RFS was available the results were highly consistent between studies with no excess between study variability present. The median RFS was 8.8 months (95% CI: 7.7–10.0 months, Fig. 1).

For OS, median values varied greatly between studies so that 90% of the variability observed was excess between study variability (Fig. 2). The pooled comparison of OS between hypomethylating agents and LDAC, across the two comparative trials, in the LDAC pre-selected subset, approached statistically significance p = 0.08 (HR = 0.87, 95% CI: 0.74-1.02). The pooled median OS was 7.5 months (95% CI: 6.1–9.2 m) and 5.4 months (95% CI: 4.4–6.7 m) for hypomethylating agents and LDAC cohorts, respectively, and 6.3 months (95% CI: 5.3–7.4 m) overall.

For 60-day mortality, the pooled estimate was 21% (95% CI: 18%–25%, Fig. 2). Results were consistent across studies, with the exception of two studies [6,8] where a markedly higher rate was observed.

3.3. Effect of age on response

The odds of response were 1.85 times higher (p = 0.001) amongst patients who were < 75 compared to those who were older (Table 4).

4. Discussion

The incidence of AML, recognized as a disease of older adults with a

Table 2
Patient Characteristics of studies included in the meta-analysis.

Study (primary author, year)	H	N	Age ≥75 (%)	Gender Male (%)	ECOG PS 0/1,2, ≥3 (%)	AML Type DN,S,M[1] (%)	Cytogenetics F,I,A[2] (%)	BM blasts median %	WBC 10^9/L median	Wheatley Group G,S,P[3] (%)
Craddock 2017	Aza	129	NR[4]	42	93,7,0	44,40,16	2,67,30	48[5]	15.6[5]	NR
Dombret 2015	Aza	241[6]	53	58	77,23,0	80,20,0	0,65,35	70	3.1	NR
Passweg 2014	Aza	45	~50[7]	60	76,18,7	NR	NR	NR	NR	NR
Cashen 2010	Dec	55	~50[7]	~50[8]	82,18,0	57,43,0	0,54,46	50	2.7	NR
Kantarjian 2012	Dec	242[9]	39	57	76,24,0	64,36,0	0,64,36	30-50	3.1	NR
Lubbert 2012	Dec	227	38	61	77,22,1	49,51,0	2,58,41	56	4.4	5,22,73
Lubbert 2016	Dec	100	~50[7]	NR	80,20[10]	35,65,0	68,32[11]	NR	NR	NR
Burnett 2007	LDAC	102	49	55	69,18,13	59,27,14	3,74,23	NR	NR	NR
Burnett 2013	LDAC	206	48	58	87,8,4	61,24,15	2,46,51	NR	< 10	3,46,50
Dennis 2015 C1	LDAC	51	51	59	86,10,4	61,29,10	3,74,24	NR	< 10	4,29,67
Dennis 2015 C2	LDAC	51	53	53	82,16,2	63,27,10	3,74,23	NR	< 10	2,33,65
Döhner 2014	LDAC	45	51	56	80,20,0	33,67,0	7,60,33	NR	5.2	2,31,67
Dombret 2015	LDAC	158	53	53	78,22,0	85,15,0	0,66,34	74	2.3	NR
Kantarjian 2012	LDAC	215	39	61	76,24,0	66,34,0	0,63,37	30-50	3.7	NR
Kantarjian 2013	LDAC	26	27	53	70,24,6	47,53,0	11,64,25	NR	NR	NR
Glasdegib	LDAC	38	61	61	53,47,0	47,53,0	8,50,42	NR	NR	NR

All percentages use the number of patients with recorded data as the denominator, percentages may not sum to 100% due to rounding for variables with 3 categories. NR: not recorded; C1: Cohort 1; C2: Cohort 2; PS: Performance Status; BM: Bone Marrow; WBC: White Blood Cell. [1]DN:*de novo*; S: Secondary; M: High-risk MDS. [2]F: Favourable; I: Intermediate; A: Adverse. [3]G: Good; S: Standard; P: Poor. [4] 63% 70 years or older. [5]mean. [6]Data for all patients who received azacitidine, demography data not presented for the 154 patients pre-selected to receive LDAC. [7]median 74–76 [8]exact number not given but text states there was an even distribution. [9]includes patients who were pre-selected to receive supportive care, data not presented by pre-selected group in this arm, 12% of the control arm received supportive care. [10]PS 2/3 combined. [11]favourable/intermediate combined.

peak in the 7th and 8th decades, appears to be increasing in recent years, possibly due to an increasing willingness of physicians to make this diagnosis in older age. Current AML treatment is based on intensive chemotherapy, which is associated with severe bone marrow, gastrointestinal, and neurological toxicities, among others. Older patients and those with comorbidities and poor performance status at diagnosis are less tolerant to this intensive therapy, and they have increased treatment-related morbidity and mortality. This population was hardly evaluated by well-controlled clinical studies prior to 2010, the time when hypomethylating agents were introduced, and therefore the treatment protocols were mainly based on physician's experience and included a variety of treatment options such as low doses of anthracyclines, variations of 7 + 3, and variations of chemotherapy combination regimens such as FLAG-IDA.

Up until recently, for patients not eligible for standard induction therapy, in particular for the ≥75-year-old patient population, there was no FDA-approved first-line therapy. In 2017, the FDA approved the use of gemtuzumab ozogamicin (GO, Mylotarg), a monoclonal antibody to CD33 linked to a cytotoxic agent, as a single-agent induction therapy in older patients with CD33 positive AML cells, based on improvement in Median OS from 3.6 in the control best supportive care arm (n = 119) to 4.9 months in the GO arm (n = 118), HR = 0.69 (95%CI: 0.53,0.90). The CR rate (best response) in the GO arm was 15.3% [32]. More recently, the FDA approved glasdegib (Daurismo), a hedgehog pathway inhibitor, in combination with LDAC in a similar population, a treatment which resulted in a CR rate of 18.2% (n = 77), compared to 2.6% (n = 38) in the LDAC alone arm, and median OS of 8.3 months compared to 4.3 months in the LDAC alone arm, HR = 0.46 (95% CI: 0.30,0.71) [8]. In addition, the FDA recently granted an accelerated approval to the BCL-2 inhibitor venetoclax (Venclexta) in combination with either LDAC or hypomethylating agents in patients age > 65 years who are unfit for intensive chemotherapy, which demonstrated tolerable toxicity and promising efficacy in single-arm studies, with CR rates of 21% (n = 61), 37% (n = 67), and 54% (n = 13) in combination with

Table 3
Outcome Data included in the meta-analysis.

Study (primary author, year)	Agent	N	CR	ORR	Median RFS (months)	Median OS (months)	60-day mortality
Craddock 2017	Azacitidine	129	NR	22%[1]	12.8[2]	8.9[3]	15%[3]
Dombret 2015	Azacitidine	154	18%	27%	8.6[1]	11.2	17%
Passweg 2014	Azacitidine	45	NR	18%	8.0[2]	6.0	18%
Cashen 2010	Decitabine	55	24%	26%	NR	7.7	20%
Kantarjian 2012	Decitabine	242[4]	16%	26%	8.3	7.7	15%
Lubbert 2012	Decitabine	227	13%	NR	NR	5.5	20%
Lubbert 2016	Decitabine	100	NR	NR	NR	6.6[5]	NR
Burnett 2007	LDAC	102	18%	NR	8.0	3.3	40%
Burnett 2013	LDAC	206	12%	19%	7.5	4.9	26%
Dennis 2015, Cohort1	LDAC	40[6]	16%	30%	9.5[2]	9.0	20%
Dennis 2015, Cohort2	LDAC	40[6]	20%	34%	6.8[2]	9.6	18%
Döhner 2014	LDAC	45	7%	13%	10.0	5.2	18%
Dombret 2015	LDAC	158	24%	26%	9.9[2]	6.4	19%
Kantarjian 2012	LDAC	215	8%	11%	6.7	5.0	20%
Kantarjian 2013	LDAC	26	4%	NR	NR	4.5	27%
Glasdegib	LDAC	38	3%	5%	NR	4.3	37%

ORR: overall response rate (CR + CRi); NR: not recorded; [1] includes marrow CR. [2] calculated amongst patients with either CR or CRi, all other studies consider only CR patients; [3] data from 108 AML patients. [4] includes patients who were pre-selected to receive supportive care, data not presented by pre-selected group in this arm, 12% of the control arm received supportive care. [5] average of decitabine alone and decitabine + ATRA arms. [6]22 patients were included in both cohorts, each cohort was weighted down to 40 patients for the meta-analysis.

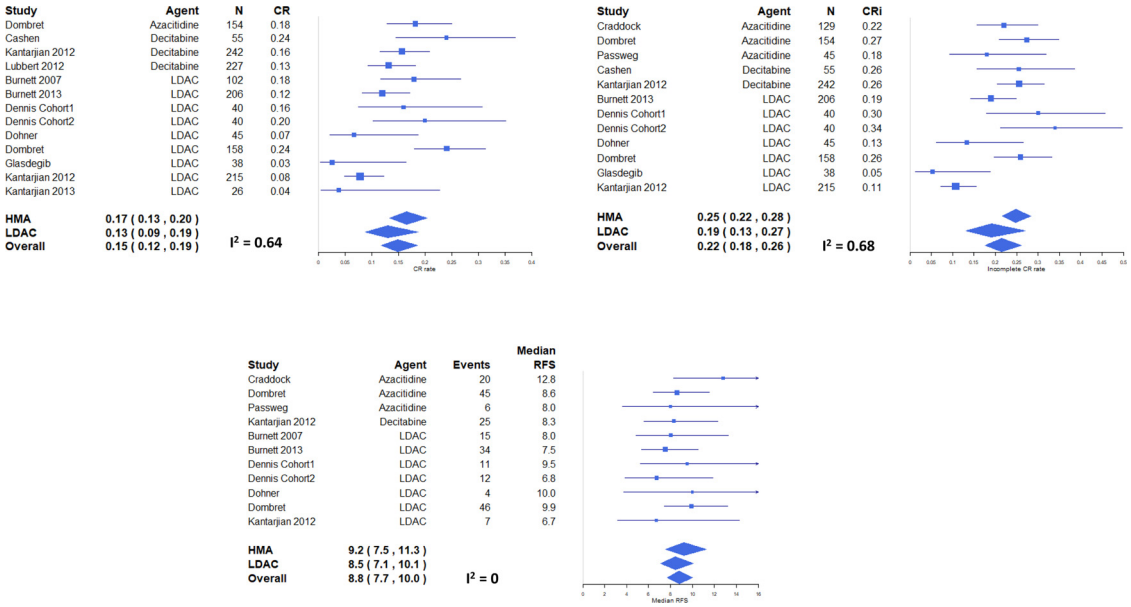

Fig. 1. Pooled analysis for CR rate, overall response rate and RFS.

LDAC, azacitidine or decitabine, respectively [7,33–35]. It should be considered, though, that patients with prior hypomethylating agent treatment for MDS were excluded from the venetoclax + hypomethylating agent study, and benefited less from the venetoclax + lDAC combination in a separate study [36].

LDAC and HMA are frequently being used as AML treatment for older and unfit patients since they are considered easier to tolerate by this population, less resource demanding on treating physicians and have acceptable efficacy. The data and analysis presented here emphasise that though extensively used in the older and unfit population, LDAC and HMA offer a modest advantage to these patients; the pooled estimate of the CR rate was only 15% (95% CI: 12%–19%) and even the best estimate for median OS, the pooled estimate for hypomethylating agents, was only 7.5 months (95% CI: 6.1–9.2 m).

With the exception of RFS, there was significant variability in the reports for all endpoints, with at least 60% of the total variability unexplained by the expected random fluctuations in outcome due to sample-size. This excess variability is indicative of the prevalence of important prognostic factors being differentially present between trials. The analyses suggest that the true estimates of outcome differ between trials and thus the random effects meta-analysis provides an estimate of the average of these different outcomes. The confidence intervals provided are thus wider than those provided by fixed effect meta-analysis, which would treat patients as having come from a single large trial.

It was decided to pool both within treatment class and across all ten trials. It's noteworthy that for CR in particular, the meta-analysis did not indicate any difference in outcome between hypomethylating agents and LDAC (p = 0.46) when pooling the two randomised comparative studies [9,10] in the subset of patients pre-selected as suitable to receive LDAC. Therefore, the overall pooled result for CR serves as a relevant benchmark when assessing the activity of future agents in this setting. Whether hypomethylating agents extend OS is somewhat controversial. It was not the primary aim of this paper, but the pooled analysis of the two randomised studies comparing a hypomethylating agent to LDAC approached statistically significance (p = 0.08, HR = 0.87) in the subset of patients pre-selected as suitable to receive LDAC. Therefore, a separate pooled estimate was provided for the median OS for both hypomethylating agents and LDAC.

Table 4
Odds ratio (95% CI) of response according to age group (< 75 v ≥75).

Study	N	Odds ratio
Burnett 2013 Clofarabine	198	1.96 (1.1,3.5)[1]
Burnett 2013 LDAC	206	1.50 (0.7,3.0)[1]
Lubbert 2012	227	2.05 (1.1,3.9)[2]
Overall		**1.85 (1.3,2.7)**

CI: confidence interval;[1] odds ratio for overall response rate (CR + CRi), [2] odds ratio for CR + PR.

A meta-analysis of decitabine outcomes has previously been reported [37] which, unlike this paper, included data from single institution studies. Single institution trials are not included here as they are likely to be more susceptible to selection bias [38,39] and results will be less generalisable. The decitabine meta-analysis [37] also included data for a decitabine schedule of 20 mg/m^2 for 10 days every 4 weeks. These studies show higher CR rates but it is not clear how much of that effect is related to schedule or selection bias, as all of the studies with this schedule were from single institution trials.

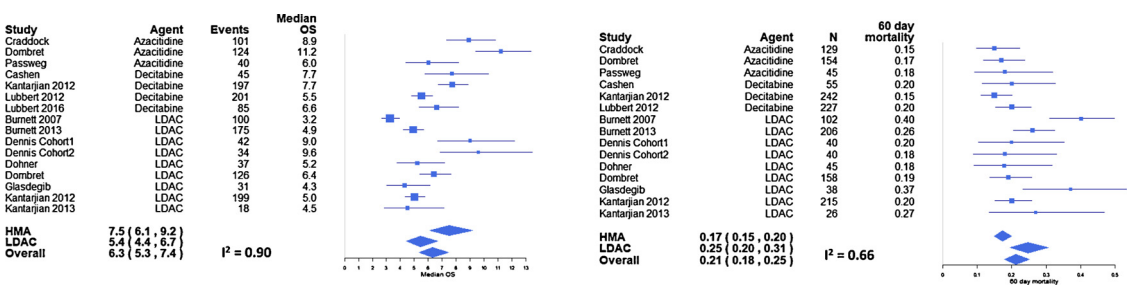

Fig. 2. Pooled analysis for OS and 60-day mortality.

Data from three studies were also included, where some patients received ATRA in combination with standard therapy. However, in the two randomised comparisons [6,11] ATRA was shown not to increase the CR rate, with conflicting results shown for OS. It is not expected therefore that the inclusion of a small percentage of patients given ATRA would have biased the results.

Data was not available for all endpoints for all studies. Median RFS could only be obtained from eight of the studies. However, results for this endpoint were remarkably consistent between studies; there was no extra between-study variability for this endpoint. This suggests that despite the fact that some studies assessed RFS in patients with a CR, and others added incomplete responders, it seemed to have little if any bearing on the pooled estimate of an 8.5-month median (95% CI: 7.4–9.7). The overall response rate (CR + CRi) was not reported for four studies, however these studies had CR rates or median OS close to the average so it seems unlikely their exclusion has biased the reported pooled estimate of incomplete CR of 22% (95% CI: 18%–26%).

For 60-day mortality, the pooled estimate was 21% (95% CI: 18%–25%) however, there was a markedly higher rate of 37% or more in two studies. This difference might partially be explained by the recruitment of patients with poor performance status (PS). In one of the studies [6], the proportion of patients recruited with a performance status of three or more was 13%, which is more than double the proportion of such patients in all other studies except one and in the other [8], the proportion of PS 2 patients was markedly higher.

OS data were the most variable between studies, with 90% of the variability being unexplained between study variability. A number of factors including age, performance status, cytogenetics, AML type (*de novo* or secondary), prior hypomethylating agent treatment for MDS, and white blood cell count, have been shown to be independently prognostic for survival outcome [1,24,26]. It is likely therefore, they are differentially present between studies and explain some of this variability. For OS, additional factors may have also contributed to the high variability; the use of effective subsequent therapies may have differed between studies, although details were not recorded often enough to assess the potential impact, and the median may not always be a good representation of average outcome for any given study. Overall, these data reinforce the need for randomised studies when assessing OS.

Finally, the relationship between age (< 75 vs. ≥ 75 years) and CR rate was assessed. Although this was available from three cohorts from two studies, this relationship was highly statistically significant ($p = 0.001$, odds ratio = 1.85) and confirmed the same findings reported for OS [1,22–26]. The decitabine meta-analysis [37] did not show that age was related to CR rate, however, this report only considered trials with decitabine and used an age cut-off of 70 years.

A noted caveat in this meta-analysis is the under representation of patients with prior hypomethylating agent treatment for MDS, as they are excluded from the majority of the studies found for the unfit AML population, including all studies with azacitidine or decitabine treatments. In the few studies which do not specifically state that this population is excluded, a separate outcome analysis is not provided. Therefore, although the population of patients with secondary AML and prior hypomethylating agent treatment for MDS is characterized by a particularly poor prognosis, with remission rates and median OS reduced by several folds [40,41], no information for a separate analysis by this baseline characteristic was found for the population of older and unfit AML patients included in this meta-analysis.

In conclusion, with any meta-analysis there are always limitations and we were as inclusive as possible so that results could be generalisable. The paucity of well controlled studies done in the older and unfit AML population, and the fact that most of the available studies were done in a relatively small population in comparison to the studies in young AML patients, emphasise the importance of a meta-analysis. In presenting the meta-analysis, the intention is to describe the data in an objective and quantified manner to provide the best available historical benchmark with LDAC and hypomethylating agents to place data from future studies in this population into context.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.leukres.2019.05.007.

References

[1] G. Juliusson, P. Antunovic, A. Derolf, et al., Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry, Blood 113 (2009) 4179–4187, https://doi.org/10.1182/blood-2008-07-172007.

[2] G. Juliusson, V. Lazarevic, A.S. Hörstedt, et al., Acute myeloid leukemia in the real world; why population-based registries are needed, Blood 119 (2012) 3890–3899, https://doi.org/10.1182/blood-2011-12-379008.

[3] I. De Kouchkovsky, M. Abdul-Hay, Acute myeloid leukemia: a comprehensive review and 2016 update, Blood Cancer J. (6) (2016) e441, https://doi.org/10.1038/bcj.2016.50.

[4] J.N. Saultz, R. Garzon, Acute myeloid leukemia: a concise review, J. Clin. Med. 5 (2016) 33, https://doi.org/10.3390/jcm5030033.

[5] H. Kantarjian, F. Ravandi, S. O'Brien, et al., Intensive chemotherapy does not benefit most older patients (age 70 years or older) with acute myeloid leukemia, Blood 116 (2010) 4422–4429, https://doi.org/10.1182/blood-2010-03-276485.

[6] A.K. Burnett, D. Milligan, A.G. Prentice, et al., A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment, Cancer 109 (2007) 1114–1124, https://doi.org/10.1002/cncr.22496.

[7] Venetoclax label, (2019) Accessed 10/05/19 https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208573s009lbl.pdf.

[8] Glasdegib Label, (2019) Accessed 10/05/19 https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210656s000lbl.pdf.

[9] H. Dombret, J.F. Seymour, A. Butrym, et al., International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with > 30% blasts, Blood 126 (2015) 291–299, https://doi.org/10.1182/blood-2015-01-621664.

[10] H.M. Kantarjian, X.G. Thomas, A. Dmoszynska, et al., Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia, J. Clin. Oncol. 30 (2012) 2670–2677, https://doi.org/10.1200/JCO.2011.38.9429.

[11] M. Lübbert, O. Grishina, C. Schmoor, et al., Results of the randomized phase II study Decider (AMLSG 14-09) comparing decitabine (DAC) with or without valproic acid (VPA) and with or without all-trans retinoic acid (ATRA) add-on in newly diagnosed elderly non-fit AML patients, Blood 128 (599) (2016).

[12] P. Fenaux, G.J. Mufti, E. Hellström-Lindberg, et al., Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia, J. Clin. Oncol. 28 (2010) 562–569, https://doi.org/10.1200/JCO.2009.23.8329.

[13] C.F. Craddock, A.E. Houlton, L.S. Quek, et al., Outcome of azacitidine therapy in acute myeloid leukemia is not improved by concurrent vorinostat therapy but is predicted by a diagnostic molecular signature, Clin. Cancer Res. 23 (2017) 6430–6440, https://doi.org/10.1158/1078-0432.CCR-17-1423.

[14] J.R. Passweg, T. Pabst, S. Blum, et al., Azacytidine for acute myeloid leukemia in elderly or frail patients: a phase II trial (SAKK 30/07), Leuk. Lymphoma 55 (2015) 87–91, https://doi.org/10.3109/10428194.2013.790540.

[15] A.F. Cashen, G.J. Schiller, M.R. O'Donnell, et al., Multicenter, phase II study of decitabine for the first-line treatment of older patients with acute myeloid leukemia, J. Clin. Oncol. 28 (2010) 556–561, https://doi.org/10.1200/JCO.2009.23.9178.

[16] M. Lübbert, B.H. Rüter, R. Claus, et al., A multicenter phase II trial of decitabine as first-line treatment for older patients with acute myeloid leukemia judged unfit for induction chemotherapy, Haematologica 97 (2012) 393–401, https://doi.org/10.3324/haematol.2011.048231.

[17] A.K. Burnett, N.H. Russell, A.E. Hunter, et al., Clofarabine doubles the response rate in older patients with acute myeloid leukemia but does not improve survival, Blood 122 (2013) 1384–1394, https://doi.org/10.1182/blood-2013-04-496596.

[18] M. Dennis, N. Russell, R.K. Hills, et al., Vosaroxin and vosaroxin plus low-dose Ara-C (LDAC) vs low-dose Ara-C alone in older patients with acute myeloid leukemia, Blood 125 (2015) 2923–2932, https://doi.org/10.1182/blood-2014-10-608117.

[19] H. Döhner, M. Lübbert, W. Fiedler, et al., Randomized, phase 2 trial of low-dose cytarabine with or without volasertib in AML patients not suitable for induction therapy, Blood 124 (2014) 1426–1433, https://doi.org/10.1182/blood-2014-03-560557.

[20] H.M. Kantarjian, G. Martinelli, E.J. Jabbour, et al., Stage I of a phase 2 study assessing the efficacy, safety, and tolerability of barasertib (AZD1152) versus low-

dose cytosine arabinoside in elderly patients with acute myeloid leukemia, Cancer 119 (2013) 2611–2619, https://doi.org/10.1002/cncr.28113.
[21] Glasdegib FDA Clinical Review, (2018) Accessed 10/05/19 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210656Orig1s000MedR.pdf.
[22] F.R. Applebaum, H. Gundacker, D.R. Head, et al., Age and acute myeloid leukemia, Blood 107 (2006) 3481–3485, https://doi.org/10.1182/blood-2005-09-3724.
[23] H.P. Erba, Prognostic factors in elderly patients with AML and the implications for treatment, Hematology Am. Soc. Hematol. Educ. Program (2007) 420–428, https://doi.org/10.1182/asheducation-2007.1.420.
[24] R. Liersch, C. Müller-Tidow, W.E. Berdel, et al., Prognostic factors for acute myeloid leukaemia in adults – biological significance and clinical use, British J Haematology 165 (2014) 17–38, https://doi.org/10.1111/bjh.12750.
[25] A. Quintas-Cardama, F. Ravandi, T. Liu-Dumlao, et al., Epigenetic therapy is associated with similar survival compared with intensive chemotherapy in older patients with newly diagnosed acute myeloid leukemia, Blood 120 (2012) 4840–4845, https://doi.org/10.1182/blood-2012-06-436055.
[26] K. Wheatley, C.L. Brookes, A.J. Howman, et al., Prognostic factor analysis of the survival of elderly patients with AML in the MRC AML11 and LRF AML14 trials, Br. J. Haematol. 145 (2009) 598–605, https://doi.org/10.1111/j.1365-2141.2009.07663.x.
[27] H. Döhner, E. Estey, D. Grimwade, et al., Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel, Blood (129) (2017) 424–447, https://doi.org/10.1182/blood-2016-08-733196.
[28] A. Whitehead, J. Whitehead, A general parametric approach to the meta-analysis of randomized clinical trials, Stat. Med. 10 (1991) 1665–1677, https://doi.org/10.1002/sim.4780101105.
[29] J.P.T. Higgins, S.J. Thompson, Quantifying heterogeneity in a meta-analysis, Stat. Med. 21 (2002) 1539–1558, https://doi.org/10.1002/sim.1186.
[30] D. Collett, Modelling Survival Data in Medical Research, Chapman and Hall, 2015.
[31] R.J. Light, D.B. Pillemer, Summing up. The Science of Reviewing Research, Harvard University Press, Cambridge MA, 1984.
[32] S. Amadori, S. Suciu, D. Selleslag, et al., Gemtuzumab ozogamicin versus best supportive care in older patients with newly diagnosed acute myeloid leukemia unsuitable for intensive chemotherapy: Results of the randomized phase III EORTC-GIMEMA AML-19 trial, J. Clin. Oncol. 34 (2016) 972–979, https://doi.org/10.1200/JCO.2015.64.0060.
[33] C.D. DiNardo, K. Pratz, V. Pullarkat, et al., Venetoclax combined with decitabine or azacitidine in treatment-naïve, elderly patients with acute myeloid leukemia, Blood 133 (2019) 7–17, https://doi.org/10.1182/blood-2018-08-868752.
[34] C.D. DiNardo, K.W. Pratz, A. Letai, et al., Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study, Lancet Oncol. 19 (2018) 216–228, https://doi.org/10.1016/S1470-2045(18)30010-X.
[35] A. Wei, S.A. Strickland, G.J. Roboz, et al., Safety and efficacy of venetoclax plus low-dose cytarabine in treatment-naïve patients aged ≥65 years with acute myeloid leukemia, Blood 128 (102) (2016).
[36] A.H. Wei, S.A. Strickland, J.Z. Hou, et al., Venetoclax combined with low-dose cytarabine for previously untreated patients with acute myeloid leukemia: results from a phase Ib/II study, J. Clin. Oncol. (2019), https://doi.org/10.1200/JCO.18.0.01600 Published online March 20,2019.
[37] P.F. He, J.D. Zhou, D.M. Yao, et al., Efficacy and safety of decitabine in treatment of elderly patients with acute myeloid leukemia: a systematic review and meta-analysis, Oncotarget 8 (2017) 41498–41507, https://doi.org/10.18632/oncotarget.17241.
[38] R. Bellomo, S.J. Warrillow, M.C. Reade, Why we should be wary of single-center trials, Crit. Care Med. 37 (2009) 3114–3119, https://doi.org/10.1097/CCM.0b013e3181bc7bd5.
[39] S. Unverzagt, R. Prondzinsky, F. Peinemann, Single-center trials tend to provide larger treatment effects than multicenter trials: a systematic review, J. Clin. Epidemiol. 66 (2013) 1271–1280, https://doi.org/10.1016/j.clinepi.2013.05.016.
[40] C. Bello, D. Yu, R.S. Komrokji, et al., Outcomes after induction chemotherapy in patients with acute myeloid leukemia arising from myelodysplastic syndrome, Cancer 117 (2011) 1463–1469, https://doi.org/10.1002/cncr.25598.
[41] T. Prébet, S.D. Gore, S. Thépot, et al., Outcome of acute myeloid leukaemia following myelodysplastic syndrome after azacitidine treatment failure, Br. J. Haematol. 157 (2012) 764–766, https://doi.org/10.1111/j.1365-2141.2012.09076.x.