A Randomised Evaluation of Low-Dose Cytosine Arabinoside plus Lenalidomide versus Single-Agent Low-Dose Cytosine Arabinoside in Older Patients with Acute Myeloid Leukaemia: Results from the LI-1 Trial

Running short title: Low-dose Ara-C and Lenalidomide in Elderly Patients with AML

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Running short title: 60/60

Abstract: 100/100

Word count (text): 1487/1500

Tables: 2

Figures: 0

Authors: 12

Reference count: 14/15

Keywords:

Acute Myeloid Leukaemia, Low-dose cytosine arabinoside, Lenalidomide, Elderly, Clinical Trial

Abstract:

Improving outcomes for older patients with acute myeloid leukaemia remains an unmet need. As part of the LI-1 trial, we evaluated lenalidomide (LEN), in combination with low-dose cytosine arabinoside (LDAC) in patients aged >60 years unfit for intensive therapy and compared this to LDAC alone. 202 patients randomised 1:1 were evaluable. Overall response rate (CR+CRi) was higher for LDAC+LEN versus LDAC (26% and 13.7%, respectively, P=0.031). However, there was no difference in overall survival between the arms (14% and 11.5% at 2 years for LDAC+LEN and LDAC, respectively). Addition of LEN was associated with increased toxicity and supportive care requirements.

INTRODUCTION

Many patients with Acute Myeloid Leukaemia (AML) diagnosed after 60 years of age are not considered suitable for intensive remission-induction chemotherapy, either due to comorbidities or frailty associated with advanced age (1). Despite treatment with either low-dose cytosine arabinoside (LDAC) or a hypomethylating agent (2, 3), survival is usually poor, with 1-year overall survival (OS) after LDAC of 21-32% in NCRI AML16 and historical arms of LI-1 (3). Combination therapy with a backbone of LDAC or hypomethylating agent with additional agents represents an attractive option, with the potential to improve patient outcomes without substantially increasing toxicity (4-7).

Recently, the BCL-2 inhibitor venetoclax has been approved, and widely adopted for the treatment of older, less fit patients with AML, in combination with either azacitidine or LDAC (4, 5). This has demonstrated superior complete remission (CR) rates compared to azacitidine or LDAC alone; 36.7% for azacytidine + venetoclax compared to 17.9% for azacitidine alone in VIALE-A (4) and 48% for LDAC + venetoclax compared to 13% for LDAC + placebo in VIALE-C (5). Improvements in survival are also seen, with median OS of 14.7 months for azacitidine + venetoclax and 9.6 months for azacytidine alone in VIALE-A and 8.4 months for LDAC + venetoclax and 4.1 months for LDAC + placebo in VIALE-C (4, 5). These survival benefits are modest, with most patients still dying of AML, and there remains a need to develop new well-tolerated, outpatient-based, effective therapeutic strategies for older, frail patients with AML to further improve outcomes.

Lenalidomide (LEN; Revlimid^{TM}), a derivative of thalidomide, is an immunomodulatory drug used to treat myeloma (8), and some cases of myelodysplastic syndrome (MDS) (9), and has potent antineoplastic, anti-angiogenic, anti-inflammatory and pro-erythropoietic properties (10). Early-phase trials of LEN in AML have demonstrated clinical activity with acceptable toxicity (11, 12).

We assessed the efficacy and tolerability of LDAC+LEN versus LDAC alone in patients aged 60+ unsuitable for intensive therapy.

METHODS

Design and Eligibility:

The LI-1 trial (ISRCTN40571019) was an international multicentre, multi-arm, randomised phase II/III trial developed to study the efficacy and tolerability of novel non-intensive therapies in AML using a "pick-a-winner" design.(6, 13) In LI-1, the comparator arm was LDAC, and there was no comparison of

different experimental arms. Patients in the LDAC control arm were recruited and randomised 1:1 with the experimental arms available contemporaneously.

Patients aged ≥60 years, with de novo or secondary AML or high-risk MDS (>10% marrow blasts), considered unfit for intensive therapy were eligible. Patients with a prior diagnosis of MDS with <10% blasts who had failed a demethylating agent, but subsequently developed AML were also eligible. Impaired renal or hepatic function (defined as serum creatinine >174μmol/L, total bilirubin ≥1.5 times upper limit of normal (ULN), aspartate aminotransferase or alanine aminotransferase ≥2.5 times ULN) were exclusion criteria. Patients with a history of myocardial infarction, unstable angina, cerebrovascular accident/transient ischaemic attack within 6 months were also excluded.

LDAC was given at 20mg BD SC on days 1-10 of each course. LEN was administered orally once daily in a flat 10mg dose for 21 days, where day 1 was day 1 of LDAC, with courses occurring at 5-week intervals for courses 1-4. Patients considered to be benefitting after 4 courses, i.e. in remission or stable disease, could continue to receive treatment until disease progression, either with LDAC+LEN at 6-week intervals, or LEN only at 4-week intervals if patient had experienced significant toxicity.

All patients provided written informed consent. The LI1 trial was sponsored by Cardiff University and approved by the Research Ethics Committee for Wales in compliance with the Declaration of Helsinki.

Endpoints and Toxicity:

The aim within the experimental arms was doubling 2-year survival from 11% to 22% (HR 0.69), with planned interim assessments after 50 and 100 patients were recruited per arm. At the first interim assessment, overall response rate (ORR), was the primary endpoint, defined as either CR or CR without evidence of adequate count recovery (CRi), and was required to be at least 2.5% higher in the experimental arm. CR was defined as normocellular marrow with <5% leukaemic blasts, evidence of normal myeloid maturation, neutrophil and platelet recovery in the absence of platelet transfusions (>$1x10^9$/L and >$100x10^9$/L, respectively). Patients in CR but failing to achieve neutrophils >$1x10^9$/L and

platelets >100x10^9/L were designated as CRi. At the second interim assessment, the primary endpoint was OS, with an HR of <0.85 in the experimental arm for the trial to continue.

The co-primary objectives at the final analysis were OS, defined as time from trial randomisation to death from any cause or last follow-up; ORR (CR+CRi) and reasons for failure, and duration of response, relapse rates and deaths in first CR. Relapse-free survival (RFS), was defined as time from remission (CR/CRi) to death or relapse, censored at last follow-up; relapse risk (RR) was defined as time from remission (CR/CRi) to relapse, censored at death in CR and last follow-up; death in CR (DCR) was defined as time from remission (CR/CRi) to death censored at relapse and last follow-up. Secondary objectives were haematological recovery times, defined as time from end of course to recovery of platelets to >100x10^9/L and neutrophils to >1x10^9/L, censored at next course, or time last known not to have been recovered; adverse events and toxicity defined by the National Cancer Institute Common Terminal Criteria for Adverse Events (NCI CTCAE) version 4; and resource usage, including number of units of blood and platelets per course; number of days on i.v. antibiotics or in hospital per course.

Statistical Analysis

All analyses are by intention-to-treat. Categorical endpoints (e.g. CR rates) were compared using logistic regression, giving odds ratios and confidence intervals. Continuous/scale variables were analysed by non-parametric (Wilcoxon rank sum) tests. Time-to-event outcomes were analysed using the log-rank test, Kaplan-Meier survival curves. Hazard ratios and 95% confidence interval were calculated using the statistics from the log-rank test.(14)

RESULTS

Patient characteristics:

Between January 2017 and June 2019, 206 patients from Denmark (8%), New Zealand (16%) and the UK (76%) were randomised (Consort Diagram; Supplementary Figure 1). Four patients were randomised in error and removed from subsequent analyses. Thus, 202 patients were evaluable. Median age was 78 years (range 62-89); 92.6% of patients were aged ≥70 years and 35.1% ≥80 years. Baseline patient demographics are shown in Table 1. Overall, 153/202 (75.7%) patients had de novo AML, 40/202 (19.8%) secondary AML and 9/202 (4.5%) high-risk MDS. Cytogenetic data was available for 173/202 patients (85.6%). One patient had favourable cytogenetics, 133 normal/intermediate and 39 adverse karyotype. Of interest, 13/202 (6.4%) patients had a del5q abnormality, but in 12/13 this was as part of a complex karyotype or in association with a *TP53* mutation. The one patient with isolated del5q was randomised to the control arm, didn't achieve CR/CRi, and died from sepsis after 2 cycles of LDAC.

The most prevalent baseline comorbidities were cardiovascular disease, infection, arrhythmias and diabetes; all affecting >10% of the study population. Less frequent comorbidities are shown in Supplementary Figure 2A. The haematopoietic cell transplantation-comorbidity index (HCT-CI) was available for 198/202 patients and was 0 in 36.1%, 1-2 in 33.1% and ≥3 in 28.7%, indicating an overall frail population (Supplementary Figure 2B).

197 patients received their allocated therapy; 100 in the LDAC arm and 97 in the LDAC+LEN arm (Supplementary Figure 1). A median of 2 courses (range 0-24; mean 3.28) was delivered in the LDAC arm and 1 course in LDAC+LEN arm (range 0-25; mean 3.48; Supplementary Figure 3).

Response:

Overall response (CR/CRi) was achieved in 40/202 patients (19.8%) (Table 2). There was a significant difference in ORR between the LDAC and LDAC+LEN arms (LDAC 13.7% and LDAC+LEN 26%, respectively, OR 0.45 [0.22, 0.93], P=0.031).

Despite the difference in ORR, 1- and 2-year OS showed no significant difference between the LDAC and LDAC+LEN arms at the second interim analysis (22.9% and 11.5% in the LDAC arm and 29.7% and

14% in the LDAC+LEN arm, respectively; HR 0.94 [0.69,1.2], P=0.719 at 2-years). Median OS was 4.6 months for LDAC vs 3.5 months for LDAC+LEN; HR 0.96 (0.71,1.30), P=0.798 (Supplementary Figure 4A). One-year OS for patients that didn't enter CR/CRi was 6.8% for LDAC+LEN vs 16.9% for LDAC (P=0.028). The most common cause of death in both arms was resistant/recurrent disease. There was no difference in survival after remission, RFS or survival after relapse between the two arms (Supplementary Figures 4B-D). Note however the study was powered to detect a difference in OS so with the low response rate observed it was unlikely differences in RFS could be detected. Analysis by AML or patient characteristics did not identify any subgroup in which LDAC+LEN had an OS benefit (Supplementary Figure 5).

Toxicity and resource usage:

Most adverse events (AEs) were grade 1/2 in both arms (Supplementary Figure 6). During cycle 1, there were 78 vs 51 grade 3/4 AEs in the LDAC+LEN and LDAC arms, respectively (P=0.02). This included 5 thrombotic events in the LDAC+LEN arm (4 grade 3 and 1 grade 4) and none in the LDAC arm. Thirty- and 60-day mortality were not significantly different between the arms (19.2% for LDAC v 19.4% for LEN+LDAC at 30 days [OR 1.02 {0.52,1.92}; p=0.96] and 31.3% v 41.2% in the LDAC v LDAC+LEN arms at 60 days [OR 1.33 {0.84,2.12}; p=0.23]; Table 2).

In course 1, supportive care requirements were higher in terms of both days of antibiotics (7 vs 3; p=0.001) and hospitalisation days (11 vs 6.5; p=0.005) for the LDAC+LEN arm (Supplementary Figure 7). There was no difference in transfusion requirements.

CONCLUSION

Despite improving the CR/CRi rate, the combination of LDAC+LEN did not improve OS, RFS or time in remission in elderly patients with AML. The addition of LEN to LDAC resulted in increased toxicity, including episodes of thrombosis, and increased supportive care requirements. Alternative strategies to improve survival for elderly patients with AML remain a significant clinical need.

Declarations

Ethics approval and consent to participate: All patients provided written informed consent. The LI1 trial was sponsored by Cardiff University and approved by the Research Ethics Committee (REC) for Wales in compliance with the Declaration of Helsinki.

Consent for publication: Not applicable

Availability of data and materials: Data from this trial will be made available upon request to the trial sponsor (Cardiff University).

Competing interests:

M.C. has received research funding from Cyclacel and Incyte, is/has been an advisory board member for Novartis, Incyte, Jazz Pharmaceuticals, Pfizer and Servier, and has received honoraria from Astellas, Novartis, Incyte, Pfizer and Jazz Pharmaceuticals. P.M. has received advisory fees and speaker honoraria from Jazz Pharmaceuticals, Pfizer, Astellas, Servier and Celgene. L.K. has received honoraria from Celgene.

Funding: We are grateful to the NIHR for supporting local trial delivery, Blood Cancer UK for research support, the Haematology Clinical Trials Unit and Centre for Trials Research, Cardiff University for managing the trial and Celgene for providing drug and additional support for this Investigator Initiated Trial.

Author Contributions: MC, MD, and the UK NCRI AML Study Group designed and implemented the trial. MD and MC were co-chief investigators; reviewed the data and wrote the manuscript. AKB designed the trial; wrote the protocol; and was chief investigator until Q3 2014; RKH: designed the trial and wrote the protocol. IFT supervised the data collection, reviewed the data. CA analysed the

data. LU and MS supervised the data collection, reviewed the data. PM, SI and LK were top recruiters in their countries. NHR: designed trial; reviewed the data. All authors reviewed the manuscript.

Acknowledgements: We are grateful to the patients for contributing to this trial. Thank you to the NIHR research teams for supporting local trial delivery and handling of patient samples.

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Table 1: Baseline clinical characteristics.

	Randomisation					
	LDAC+ Lenalidomide		LDAC		Total	
	N=100		N=102		N=202	
Age at entry (years)						
Mean (SD)	77.5	(5.3)	77.2	(5.5)	77.3	(5.4)
Median (IQR)	77.7	(73.5, 81.1)	77.5	(73.4, 81.2)	77.7	(73.4, 81.2)
Min, max		(62.2, 89.1)		(63.1, 92.2)		(62.2, 92.2)
Missing (%)	0	(0.0)	0	(0.0)	0	(0.0)
Age group (years)						
60-64	2	(2.0)	1	(1.0)	3	(1.5)
65-69	4	(4.0)	8	(7.8)	12	(5.9)
70-74	29	(29.0)	27	(26.5)	56	(27.7)
75-79	28	(28.0)	32	(31.4)	60	(29.7)
80+	37	(37.0)	34	(33.3)	71	(35.1)
Missing (%)	0	(0.0)	0	(0.0)	0	(0.0)
Sex						
Female	46	(46.0)	39	(38.2)	85	(42.1)
Male	54	(54.0)	63	(61.8)	117	(57.9)
Missing (%)	0	(0.0)	0	(0.0)	0	(0.0)
WHO performace status						
0	15	(15.0)	15	(14.7)	30	(14.9)
1	58	(58.0)	59	(57.8)	117	(57.9)
2	22	(22.0)	23	(22.5)	45	(22.3)
3	5	(5.0)	5	(4.9)	10	(5.0)
Missing (%)	0	(0.0)	0	(0.0)	0	(0.0)
AML type						
De novo	75	(75.0)	78	(76.5)	153	(75.7)
Secondary	21	(21.0)	19	(18.6)	40	(19.8)
High risk MDS	4	(4.0)	5	(4.9)	9	(4.5)
Missing (%)	0	(0.0)	0	(0.0)	0	(0.0)
WBC categories (10^9/L)						
0.0 - 9.9	66	(66.0)	67	(65.7)	133	(65.8)
10.0 - 49.9	25	(25.0)	29	(28.4)	54	(26.7)
50 - 99.9	7	(7.0)	5	(4.9)	12	(5.9)
100+	2	(2.0)	1	(1.0)	3	(1.5)
Missing (%)	0	(0.0)	0	(0.0)	0	(0.0)
Cytogenetic status						
Favourable	0	(0.0)	1	(1.0)	1	(0.5)
Normal/Intermediate	63	(63.0)	70	(68.6)	133	(65.8)
Adverse	17	(17.0)	22	(21.6)	39	(19.3)
Unknown	20	(20.0)	9	(8.8)	29	(14.4)
Missing (%)	0	(0.0)	0	(0.0)	0	(0.0)
Wheatley Index						
Good	3	(3.0)	2	(2.0)	5	(2.5)
Standard	47	(47.0)	42	(41.2)	89	(44.1)
Poor	50	(50.0)	58	(56.9)	108	(53.5)
Missing (%)	0	(0.0)	0	(0.0)	0	(0.0)

Abbreviations: LDAC; low-dose cytosine arabinoside, SD; standard deviation, IQR; interquartile range, AML; acute myeloid leukaemia, MDS; myelodysplastic syndrome, WBC; white blood cell count.

Table 2: Response and survival outcomes. Response endpoints are reported as n (%) and odds ration comparing LDAC to LDAC+LEN. Survival endpoints are reported as Kaplan-Meier estimates (%) and hazard ratios comparing LDAC+LEN to LDAC.

	Randomisation			
	LDAC+Lenalidomide	LDAC	OR/HR (95% CI)	P value
	N=100	N=102		
Patient status, n(%)				
Resistant disease	55 (55.0)	69 (67.6)	1.71 (0.97, 3.03)	0.066
Induction death	19 (19.0)	19 (18.6)	0.98 (0.48, 1.98)	0.946
Achieved CR/CRi	26 (26.0)	14 (13.7)	0.45 (0.22, 0.93)	0.031
Response outcomes n(%)				
CR	24 (24.0)	12 (11.8)	0.42 (0.20, 0.90)	0.026
CRi	2 (2.0)	2 (2.0)	0.98 (0.14, 7.10)	0.984
ORR (CR+CRi)	26 (26.0)	14 (13.7)	0.45 (0.22, 0.93)	0.031
Survival endpoints (months)				
Median survival	3.5	4.6		
30 day mortality	19.4	19.2	1.02 (0.54, 1.92)	0.957
60 day mortality	41.2	31.3	1.33 (0.84, 2.12)	0.225
1 year survival	29.7	23.3	0.94 (0.68, 1.31)	0.732
2 year survival	14.3	11.1	0.95 (0.70, 1.29)	0.730
1 year relapse free survival	57.7	35.7	1.26 (0.52, 3.02)	0.611
2 year relapse free survival	30.8	14.3	1.57 (0.77, 3.22)	0.220
2 year survival after remission	45.8	35.7	0.66 (0.27, 1.61)	0.322
1 year survival after relapse	22.2	20.0	1.53 (0.65, 3.63)	0.351
1 year survival no CR/CRi	6.8	17.3	1.47 (1.04, 2.09)	0.024

Abbreviations: LDAC; low-dose cytosine arabinoside, OR; odds ratio, HR; hazard ratio, CR; complete response, CRi; complete response with incomplete recovery of counts, ORR; overall response rate.