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SHORT REPORT

Haematological Malignancy – Clinicals

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

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Summary

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. Two hundred and two 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). The addition of LEN was associated with increased toxicity and supportive care requirements.

KEYWORDS
acute myeloid leukaemia, clinical trial, elderly, lenalidomide, low-dose cytosine arabinoside

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 a 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 a median OS of 14.7 months for azacitidine + venetoclax, 9.6 months for azacytidine alone in VIALE-A, 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™), a derivative of thalidomide, is an immunomodulatory drug used to treat myeloma[8] and some cases of myelodysplastic syndrome (MDS),[9] and has potent anti-neoplastic, 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, multiarm, 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 >174 μmol/L, total bilirubin ≥1.5 times the 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 20 mg BD SC on days 1–10 of each course. LEN was administered orally once daily in a flat 10 mg 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 four courses, that is 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 the 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.

End-points 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 end-point, 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 ($>1\times10^9$/L and $>100\times10^9$/L respectively). Patients in CR but failing to achieve neutrophils $>1\times10^9$/L and platelets $>100\times10^9$/L were designated as CRi. At the second interim assessment, the primary end-point 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; duration of response; relapse rates; and deaths in the 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 $>100\times10^9$/L and neutrophils to $>1\times10^9$/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 intravenous antibiotics or in hospital per course.

Statistical analysis

All analyses are by intention-to-treat. Categorical end-points (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 and Kaplan–Meier survival curves. Hazard ratios and 95% confidence intervals 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 United Kingdom (76%) were randomised (Consort Diagram; Figure S1). Four patients were randomised in error and removed from subsequent analyses. Thus, 202 patients were evaluable. The 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 were available for 173/202 patients (85.6%). One patient had favourable cytogenetics, 133 normal/intermediate and 39 adverse karyotypes. 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, did not achieve CR/CRi and died from sepsis after two 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 Figure S2A. 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 (Figure S2B).

One hundred and ninety-seven patients received their allocated therapy: 100 in the LDAC arm and 97 in the LDAC + LEN arm (Figure S1). A median of two courses (range 0–24; mean 3.28) was delivered in the LDAC arm and one course in the LDAC + LEN arm (range 0–25; mean 3.48; Figure S3).

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 versus 3.5 months for LDAC + LEN; HR 0.96 (0.71, 1.30), $p = 0.798$ (Figure S4A). One-year OS for patients that did not enter CR/CRi was 6.8% for LDAC + LEN versus 16.9% for LDAC ($p = 0.028$). The most common cause of death in both arms was a resistant/recurrent disease. There was no difference in survival after remission, RFS or survival after relapse between the two arms (Figure S4B–D). Note, however, that 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 (Figure S5).

Toxicity and resource usage

Most adverse events (AEs) were grade 1/2 in both arms (Figure S6). During cycle 1, there were 78 versus 51 grade 3/4 AEs in the LDAC + LEN and LDAC arms respectively ($p = 0.02$). This included five 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 vs. 19.4% for LEN + LDAC at 30 days [OR 1.02 {0.52, 1.92}; $p = 0.96$] and 31.3% vs. 41.2% in the LDAC vs. 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 (Figure S7). 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.

AUTHOR CONTRIBUTIONS

Mhairi Copland, Mike Dennis and the UK NCRI AML Study Group designed and implemented the trial. Mike Dennis and Mhairi Copland were co-chief investigators; they reviewed the data and wrote the manuscript. Alan K. Burnett designed the trial, wrote the protocol and was chief investigator until Q3 2014; Robert K. Hills designed the trial and wrote the protocol. Ian F. Thomas supervised the data collection and reviewed the data. Cono Ariti analysed the data. Laura Upton and Mia Sydenham supervised the data collection and reviewed the data. Priyanka Mehta, Shahid Islam and Lars Kjeldsen were the top recruiters in their

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

TABLE 2 Response and survival outcomes.

	Randomisation			
	LDAC + Lenalidomide	LDAC		
	N = 100	*N* = 102	OR/HR (95% CI)	*p* value
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 end-points (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

Note: Response end-points are reported as *n* (%) and the odds ratio comparing LDAC to LDAC + LEN. Survival end-points are reported as Kaplan–Meier estimates (%) and hazard ratios comparing LDAC + LEN to LDAC.

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

countries. Nigel Russell: designed the trial; reviewed the data. All authors reviewed the manuscript.

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CONFLICT OF INTEREST STATEMENT

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.

DATA AVAILABILITY STATEMENT

Data from this trial will be made available upon request to the trial sponsor (Cardiff University).

ETHICS STATEMENT

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.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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