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ORIGINAL ARTICLE

A randomised comparison of the novel nucleoside analogue sapacitabine with low-dose cytarabine in older patients with acute myeloid leukaemia

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The development of new treatments for older patients with acute myeloid leukaemia (AML) is an active area, but has met with limited success. Sapacitabine is a novel orally administered nucleoside analogue that has shown encouraging activity in unrandomised early-stage trials. We randomised 143 untreated patients with AML or with high-risk myelodysplastic syndrome (>10% marrow blasts) between sapacitibine and low-dose ara-C (LDAC) in our 'Pick a Winner' trial design. At the planned interim analysis there was no difference between LDAC and sapacitibine in terms of remission rate (CR/CRi, 27% vs 16% hazard ratio (HR) 1.98(0.90–4.39) $P=0.09$), relapse-free survival (10% vs 14% at 2 years, HR 0.73(0.33–1.61) $P=0.4$) or overall survival (OS; 12% vs 11% at 2 years, HR 1.24(0.86–1.78) $P=0.2$). Sapacitibine was well tolerated, apart from more grade 3/4 diarrhoea. On the basis of these findings sapacitibine did not show sufficient evidence of benefit over LDAC for the trial to be continued.

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INTRODUCTION

There has been increasing interest in developing new treatments for older patients with acute myeloid leukaemia (AML) in recognition of the increasing importance of this patient group based on demographic changes, and as there remains a major unmet clinical need. Ideally, such treatment should be well tolerated, requiring minimal hospitalisation and, for convenience, should be orally available. Several attempts have been made, but so far with limited success.[1–8]

Sapacitabine (also known as CS-682, CYC682) is a rationally designed 2′-deoxycytidine-type nucleoside analogue that can be administered orally.[9] When compared with other nucleoside analogues, sapacitabine is unique in its ability to induce cell cycle arrest at the G2 phase and in causing single-strand DNA breakage that is irreparable by ligation.[10] Following oral administration, sapacitabine is converted to 1-(2-*C*-cyano-2-deoxy-*β*(-D-arabino-pentafuranosyl) cytosine (CNDAC) by amidases and esterases in the gut, plasma and liver.[11] CNDAC is further converted to CNDAC-mono phosphate by deoxycytidine kinase and this is thought to be the rate-limiting step in the formation of CNDAC-triphosphate, the most active metabolite in terms of cytotoxicity. CNDAC-phosphates are degraded by cytidine deaminase and 5′nucleotidase.[12] Both sapacitabine and CNDAC are active against a wide range of human cancer cell lines *in vitro* and animal models *in vivo*.

The first studies conducted by the MD Anderson Group in older untreated or relapsed patients confirmed tolerability and efficacy.[13] In the randomised phase 2 study three schedules were tested (200 or 300 mg b.i.d. for 7 days or 400 mg b.i.d. for 3 days per week for 2 weeks, with each schedule being repeated every 3–4 weeks[14]). As these studies demonstrated that the drug was active, well tolerated in older patients and orally available, we incorporated it as an option to prospectively test it as first-line treatment for older patients.

MATERIALS AND METHODS

The aim of the study was to compare a 1:1 randomisation of low-dose ara-C (LDAC) with sapacitabine in older patients who were not considered suitable for intensive therapy. LDAC treatment comprised Ara-C 20 mg b.i.d. for 10 days by subcutaneous injection for 4 courses 4–6 weeks apart. Sapacitabine was given orally 300 mg b.i.d. for 3 consecutive days in weeks 1 and 2, which was repeated after 4 weeks. Six courses were intended. Patients on either treatment who were considered by their investigator to be benefiting were permitted to undergo more courses. Patients were required to give written consent. The trial was sponsored by Cardiff University and approved by the Wales Research Ethics Committee in compliance with the Declaration of Helsinki.

Initially the randomisation was part of the AML16 trial (ISRCTN 11036523) as part of our 'Pick a Winner' trial strategy.[15] When AML16 closed in November 2011, the randomisation was carried forward into the LI-1 trial (ISRCTN40571019). The eligibility criteria for the randomisation remained the same in both trials and included *de novo* and secondary AML and high-risk myelodysplastic syndrome, which was defined as >10% marrow blasts.

The Pick a Winner design is a multi-arm multi-stage randomised comparison of several treatments against a common control arm. There are two early assessment points at which arms can be closed for futility. In the context of the AML16 and LI-1 trials the aim is to double 2-year survival from 11 to 22%. For each comparison, 340 events are required to give just <80% power at $P=0.01$ (to allow for multiple comparisons) after building in two interim futility analyses. On the basis of the characteristics of the compound being tested, these either take place after 50 and 100 patients

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have been recruited to each arm (requiring increases in remission rate of 2.5% and 7.5%, respectively, for the comparison to continue), or after a total of 85 and 170 deaths have been observed (requiring a hazard ratio (HR) on survival <1 and 0.85, respectively). The latter approach was used for sapacitabine as it was felt that improving remission in this case would not be a prerequisite for improving survival. As such, recruitment to the first stage continued beyond 50 patients per arm to reduce the time required for the necessary number of events to accumulate.

The reasons why patients were not considered suitable for intensive treatment and details of comorbidity (using the Sorror index components)[16] were collected at entry. Patients were categorised using the validated multi-parameter Wheatley risk score,[17] which is based on age, performance score, cytogenetics and *de novo* or secondary disease, and has been prospectively validated in older patients who received LDAC. Diagnosis was made locally, and response definitions as described below were allocated by the local investigator. Cytogenetic (>20 metaphases) and immunophenotypic characterisation was carried out in regional reference laboratories that participate in national quality assurance schemes.

Toxicity

Adverse events and toxicity were recorded as defined by the National Cancer Institute Common Toxicity Criteria Version 3.

Definitions of end points

The protocol defined complete remission (CR) as a normo-cellular bone marrow aspirate containing $<5\%$ leukaemic blasts and showing evidence of normal maturation of other marrow elements. Persistence of myelodysplastic features did not preclude the diagnosis of CR. Although not in the original protocol, in this report, to achieve CR, patients required neutrophil recovery to 1.0×10^9/l and platelets to 100×10^9/l, without evidence of extramedullary disease. Patients who achieved CR according to the protocol but without count recovery are denoted here as CRi.

Following international guidelines,[18] overall survival (OS) is defined as the time from randomisation to death. For remitters, relapse-free survival is the time from remission (CR or CRi) until relapse or death. Survival from CR is defined as the time from CR/CRi (first report) until death. Survival percentages are quoted at 2 years, with 1-year survival in patients not achieving CR because of small numbers at 2 years.

Statistical methods

All analyses are by intention-to-treat. Follow-up is complete to 1 January 2014 for patients entering AML16, and to 1 October 2013 for patients entering the LI-1 trial. Surviving patients are censored at the date last known to be alive. Median follow-up for survival is 26 months (longest survivor 39 months).

Categorical end points (for example, CR rates) were compared using Mantel–Haenszel tests, giving Peto odds ratios (OR) and confidence intervals. Continuous variables were analysed by parametric (*t*-test) or nonparametric (Wilcoxon rank sum) tests as appropriate. Time-to-event outcomes were analysed using the log-rank test, with Kaplan–Meier survival curves. OR/HR <1 indicate benefit for the investigational therapy (sapacitabine).

For analyses of outcomes such as CR, survival, relapse-free survival and so on, in order to take into account the fact that recruitment took place as part of two trials, effect sizes and confidence intervals are given for the effect of sapacitabine stratified for trial protocol, and tests for interaction between treatment and trial are also given in all results. Survival data are calculated on pooled data.

In addition to overall analyses, exploratory subgroup analyses were performed by the randomisation stratification parameters and other important variables, with suitable tests for interaction. Because of the well-known dangers of subgroup analysis, these were interpreted cautiously.

In October 2012, the Data Monitoring and Ethics Committee (DMEC) met to review data on 143 patients randomised, after 88 events had been observed. The requirement at this stage for continuation was for an HR less than 1. The observed HR for survival was 1.23 (95% CI 0.81–1.88, $P=0.3$). At this point the conditional power to reach significance at $P=0.01$ was 9% and that to reach significance at $P=0.05$ was 15% using a design characteristic of looking for an HR of 0.69. As this HR exceeded 1, the DMEC recommendation was to close this randomisation.

RESULTS

Between August 2010 and November 2011, 82 patients were randomised as part of the NCRI AML16 trial (ISRCTN 11036523), and between January 2012 and September 2012 a total of 61 patients were randomised as part of the UK Leukaemia and Lymphoma Research LI-1 trial (ISRCTN40571019). The data from both trials remained confidential to all except the DMEC until the final analysis.

The characteristics of the patients are shown on Table 1 and the treatment disposition in Figure 1 (CONSORT diagram). The median age of all randomised patients was 75 years (range 54–88); 3.5% of patients were <65years and 81% were $\geqslant75$ years; 59% had *de novo* AML, 26% had secondary disease and 15% had high-risk myelodysplastic syndrome. Secondary disease was for LDAC ($n=20$: 9 AHD, 1 t-AML, 5 both; 5 unknown) and for sapacitibine ($n=17$: 13 AHD, 1 t-AML, 2 both, 1 unknown). The reasons given for not receiving intensive therapy were age in 77% of cases, fitness in 56% of cases (both together in 39% of cases) and other reasons in 9% of cases (patient choice accounting for more than half of such decisions, with the remaining decisions owing to the presence of comorbidities). Of the 143 patients randomised the median number of treatment courses given was 3 for LDAC (mean 3.0, 0 = 4%, 1 = 30%, 2 = 14%, 3 = 8%, 4 = 26%, 5 = 7%, 6 = 4%, 7 = 1%, 8 = 5%) and 2 for sapacitabine (mean 2.9,0 = 1%,1 = 34%,2 = 24%, 3 = 9%, 4 = 13%, 5 = 3%, 6 = 9%, 7 = 1%, 8 = 6%). The distribution of patients by the multi-parameter risk score (Wheatley score) was 4% good risk, 36% standard risk and 60% poor risk. This validated score predicted a 12-month survival of 36%, 42% and 14% for LDAC, respectively, in the three risk groups. Of the comorbidities listed, the most frequent were those described as cardiac, in 33% of patients.

Response

The overall response rate for all was 22% (CR 17%; CRi 5%) and survival at 12 and 24 months was 27 and 11%. Of the 73 patients randomised to LDAC, 21% achieved CR and 7% achieved CRi, which was not significantly different from the 70 patients allocated to sapacitabine (CR 13%; CRi 3%; stratified OR for CR 1.72 (0.72–4.12) $P=0.2$; stratified OR for CR/CRi 1.98 (0.90–4.39) $P=0.09$; Table 2). The protocol specified a narrow assessment of remission status after each course until remission status was established. The median time to response was 89 days for both LDAC and sapacitabine; the median number of courses given before CR was 2.5 for LDAC and 2 for sapacitabine. Although there was a trend for an increased 30- and 60-day mortality in the sapacitabine arm, the difference was not significant (15% vs 16%, pooled $P=0.9$ and 23% vs 32% pooled $P=0.3$), and there was no heterogeneity in response between the risk groups.

Toxicity

The grade 3 and 4 toxicities that were reported in $>10\%$ of patients, expressed as per course received, are shown in Figure 2, wherein it can be seen that diarrhoea was more frequent among spacitabine patients. There were no significant differences in resource usage with the exception of more days on antibiotics in course 1 and day visits to hospital after course 2 among sapacitibine patients (Table 3), although figures were consistently higher for sapacitabine.

Outcome of nonresponders

The median OS of patients who did not achieve CR/CRi was 3.9 months and was not significantly different between the 53 LDAC (median OS 4.8 months) and 59 sapacitabine patients (median survival 3.7 months) (stratified HR 1.20 (0.80–1.80) $P=0.4$) (Figure 3a).

Table 1. Patient characteristics

Characteristic	*Overall*		*AML16*		*LI-1*	
	LDAC (n = *73*)	*Sapacitabine* (n = *70*)	*LDAC* (n = *42*)	*Sapacitabine* (n = *40*)	*LDAC* (n = *31*)	*Sapacitabine* (n = *30*)
Age						
< 60	1 (1%)	0	1 (2%)	0	0	0
60–64	3 (4%)	1 (1%)	1 (2%)	1 (3%)	2 (6%)	0
65–69	12 (16%)	10 (14%)	7 (17%)	6 (15%)	5 (16%)	4 (13%)
70–74	20 (27%)	22 (31%)	10 (24%)	11 (28%)	10 (32%)	11 (37%)
75–79	25 (34%)	18 (26%)	14 (33%)	10 (25%)	11 (35%)	8 (27%)
80+	12 (16%)	19 (27%)	9 (21%)	12 (30%)	3 (10%)	7 (23%)
Median (range)	75 (54–84)	75 (62–88)	76 (54–84)	76 (62–88)	74 (60–82)	75 (65–85)
Sex						
Female	27 (37%)	22 (31%)	17 (40%)	11 (28%)	10 (32%)	11 (37%)
Male	46 (63%)	48 (69%)	25 (60%)	29 (73%)	21 (68%)	19 (63%)
Diagnosis						
De Novo	44 (60%)	41 (59%)	26 (62%)	23 (58%)	18 (58%)	18 (60%)
Secondary	20 (27%)	17 (24%)	11 (26%)	9 (23%)	9 (29%)	8 (27%)
High risk MDS	9 (12%)	12 (17%)	5 (12%)	8 (20%)	4 (13%)	4 (13%)
WBC ($x10^9$/l)						
< 10	41 (56%)	42 (60%)	22 (52%)	22 (55%)	19 (61%)	20 (67%)
10–49.9	21 (29%)	21 (30%)	13 (31%)	13 (33%)	8 (26%)	8 (27%)
50–99.9	5 (7%)	4 (6%)	4 (10%)	3 (8%)	1 (3%)	1 (3%)
100+	6 (8%)	3 (4%)	3 (7%)	2 (5%)	3 (10%)	1 (3%)
Median (range)	8.3 (0.5–336)	5.3 (0.3–177.5)	9.5 (0.5–127)	8.0 (0.3–177.5)	8.0 (0.5–336)	3.3 (0.9–109.6)
Performance Status						
WHO PS 0	20 (27%)	19 (27%)	15 (36%)	13 (33%)	5 (16%)	6 (20%)
WHO PS 1	40 (55%)	35 (50%)	20 (48%)	18 (45%)	20 (65%)	17 (57%)
WHO PS 2	9 (12%)	11 (6%)	6 (14%)	6 (15%)	3 (10%)	5 (17%)
WHO PS 3,4	4 (5%)	5 (7%)	1 (2%)	3 (8%)	3 (10%)	2 (7%)
Cytogenetics						
Favourable	1 (2%)	0	0	0	1 (5%)	0
Intermediate	39 (78%)	33 (75%)	26 (84%)	21 (75%)	13 (68%)	12 (75%)
Adverse	10 (2%)	11 (25%)	5 (16%)	7 (25%)	5 (26%)	4 (25%)
Unknown	23	23	11	12	12	14
Wheatley Group						
Good	1 (1%)	4 (6%)	0	2 (5%)	1 (3%)	2 (7%)
Standard	28 (38%)	24 (34%)	17 (40%)	15 (38%)	11 (35%)	9 (30%)
Poor	44 (60%)	42 (60%)	25 (60%)	23 (58%)	19 (61%)	19 (63%)
Comorbidity						
Arrhythmia	6/70 (9%)	14/67 (21%)	2/40 (5%)	9/39 (23%)	4/30 (13%)	5/28 (18%)
Cardiac	19/71 (27%)	27/67 (40%)	13/42 (31%)	21/39 (54%)	6/30 (20%)	6/28 (21%)
Cerebrovascular	4/71 (6%)	5/68 (7%)	4/40 (10%)	4/40 (10%)	0/31	1/28 (4%)
Diabetes	14/72 (19%)	11/68 (16%)	9/41 (22%)	7/40 (18%)	5/31 (16%)	4/28 (14%)
Mild hepatic	5/71 (7%)	2/67 (3%)	3/40 (8%)	2/40 (5%)	2/31 (6%)	0/27
Severe hepatic	0/71	1/67 (1%)	0/42	1/40 (3%)	0/31	0/27
Heart valve disease	1/72 (1%)	0/68	0/42	0/40	1/31 (3%)	0/28
Inflammatory bowel	3/73 (4%)	2/68 (3%)	1/40 (3%)	1/40 (3%)	2/31 (6%)	1/28 (4%)
Infection	11/72 (15%)	10/67 (15%)	7/41 (17%)	9/40 (23%)	4/31 (13%)	1/27 (4%)
Obesity	9/72 (13%)	5/68 (7%)	6/41 (15%)	2/40 (5%)	3/31 (10%)	3/28 (11%)
Peptic ulcer	2/72 (3%)	2/68 (3%)	1/41 (2%)	1/40 (3%)	1/31 (3%)	1/28 (4%)
Prior tumour	6/72 (8%)	4/68 (6%)	4/41 (10%)	1/40 (3%)	2/31 (6%)	3/28 (11%)
Psychiatric	3/71 (4%)	4/68 (6%)	3/40 (8%)	0/40	0/31	4/28 (14%)
Moderate pulmonary	3/68 (4%)	10/64 (16%)	2/38 (5%)	6/37 (16%)	1/30 (3%)	4/27 (15%)
Severe pulmonary	3/69 (4%)	5/64 (8%)	2/38 (5%)	5/37 (14%)	1/31 (3%)	0/27
Renal	3/70 (4%)	3/68 (4%)	2/40 (5%)	3/40 (8%)	1/31 (3%)	0/28
Rheumatological	15/72 (21%)	12/68 (18%)	13/41 (32%)	5/40 (13%)	2/31 (6%)	7/28 (25%)
Reason for NI						
Age	54/72 (75%)	54/68 (79%)	29/41 (71%)	32/40 (80%)	25/31 (81%)	22/28 (79%)
Fitness	38/72 (53%)	40/68 (59%)	29/41 (71%)	28/40 (70%)	9/31 (29%)	12/28 (43%)
Age and fitness	22/72 (31%)	32/68 (47%)	17/41 (41%)	23/40 (58%)	5/31 (16%)	9/28 (32%)
Other	7/72 (10%)	6/68 (9%)	5/41 (12%)	3/40 (8%)	2/31 (6%)	3/28 (11%)
Patient choice	3	4	1	2	2	2
No inpatient stay	0	1	0	0	0	1
Cardiac	2	0	2	0	0	0
COPD	1	0	1	0	0	0
Misc comorbidities	0	1	0	1	0	0
Only option open	1	0	1	0	0	0

Abbreviations: AML, acute myeloid leukaemia; COPD, chronic obstructive pulmonary disease; LDAC, low-dose ara-C; MDS, myelodysplastic syndrome; NI, non-intensive.

Survival of responders

In the 31 patients who achieved a CR/CRi the median survival from time of response was 13.2 months, but there was no difference between the treatment arms (stratified HR 1.00 (0.39–2.56) $P = 1.0$; Figure 3b). When comparing patients who achieved CR with those who achieved CRi, there was no significant difference overall ($P = 0.2$), although patients with a CR had a longer median survival (13.2 months vs 9.5 months).

Survival from relapse

Following relapse there was some evidence of better survival among patients treated with LDAC than with sapacitabine (2-year survival 46% vs 8%, stratified HR 3.86 (0.90–16.67) $P = 0.07$; Figure 3c).

OS

As the outcome of remitters and nonremitters did not differ between the treatments, it is unsurprising that neither relapse-free survival (median 7.1 months vs 7.0 months) (Figure 3d) nor OS (median 4.7 months vs 5.9 months) (Figure 3e) was significantly different between the treatment arms at 2 years.

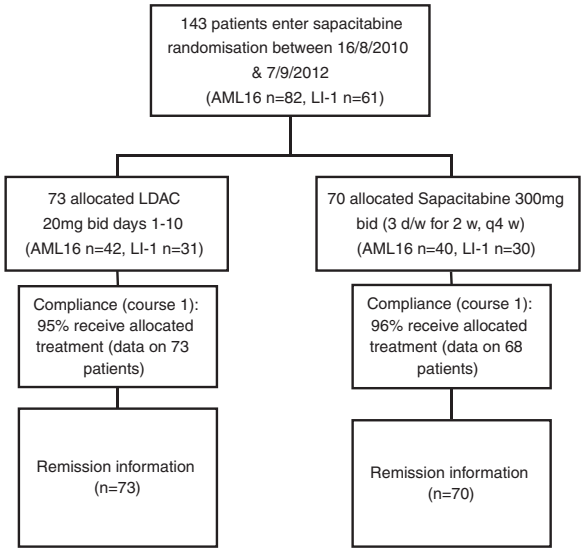

Figure 1. CONSORT diagram for trial.

Subgroup analysis

Exploratory analyses were carried out to find out whether there was an identifiable subgroup with a differential response. Notably there was no heterogeneity by trial (Supplementary Figure 1; Table 2). Baseline covariates including age, sex, diagnosis, cytogenetics, white blood count, performance status and Wheatley risk group were explored (Supplementary Figures 2 and 3) There was some evidence of significant interactions between treatment and diagnosis and white blood count on OS, but in no subgroup was there evidence of a benefit for sapacitabine.

DISCUSSION

Older patients with AML present an important challenge in several respects. In many cases it is concluded that they are not likely to benefit from intensive therapy.[19–21] This may be because it is perceived by the physician or the patients that the traditional '3+7'-like approach will possibly shorten life, or because adverse features such as adverse cytogenetics or secondary disease has a low chance of providing a remission, or one of any useful duration. Some patients who may be able to withstand an intensive approach may be reluctant to invest in the likely morbidity and hospitalisation if there is an alternative. Some patients may lack the social back-up required for an intensive approach. An important component in this decision is the physician. In our previous AML14 trial we planned to randomise older patients to an intensive or nonintensive approach. Of 1485 patients in the trial, only eight were randomised.[22] When examining the variables that were associated with the decision on treatment modality in centres where both were available, the physician emerged as a significant independent factor in multivariable analysis after performance score and age.

Efforts have been made to develop scoring systems to indicate more accurately the prospects for patient groups.[16,17,23] Several of these were derived from data sets in which patients only had an intensive treatment on offer. Few have been prospectively validated, and, although they have prognostic utility, they are not predictive. Epidemiological data and older small clinical trial data suggest that patients who receive intensive therapy will survive better;[24] nevertheless, there are a substantial proportion of patients, mostly, as in this trial, over 70 years, who choose, or are advised to accept, a nonintensive approach. Historically, such patients may have received only supportive care. Given that this population is going to increase based on demographic changes and increased aspirations, they become a priority group requiring therapeutic improvement who have seldom been the focus of collaborative group trials.

Table 2. Outcomes for patients by randomised allocation—overall, results stratified by trial

	LDAC, %	*Sapa, %*	*HR/OR, 95% CI*	P-*value*	P-*value for heterogeneity between AML16, LI-1*
CR	21	13	1.72 (0.72–4.12)	0.2	0.6
CRi	7	3			
ORR (CR+CRi)	27	16	1.98 (0.90–4.39)	0.09	0.6
Resistant disease	58	69	1.59 (0.81–3.13)	0.2	0.8
Induction death	15	16	1.05 (0.42–2.59)	0.9	0.6
30-day mortality	15	16	1.04 (0.45–2.41)	0.9	0.7
60-day mortality	23	32	1.40 (0.74–2.63)	0.3	0.7
2-year survival	12	11	1.24 (0.86–1.78)	0.2	0.6
2-year RFS	10	14	0.73 (0.33–1.61)	0.4	0.4
2-year survival from CR	31	16	1.22 (0.48–3.09)	0.7	0.9
2-year survival from relapse	46	8	3.86 (0.90–16.67)	0.07	0.4
1-year survival for non-CR	19	17	1.09 (0.73–1.62)	0.7	0.4

Abbreviations: CR, complete remission; HR, hazard ratio; OR, odds ratio; ORR, overall response rate; RFS, relapse free survival. Percentages are pooled percentages.

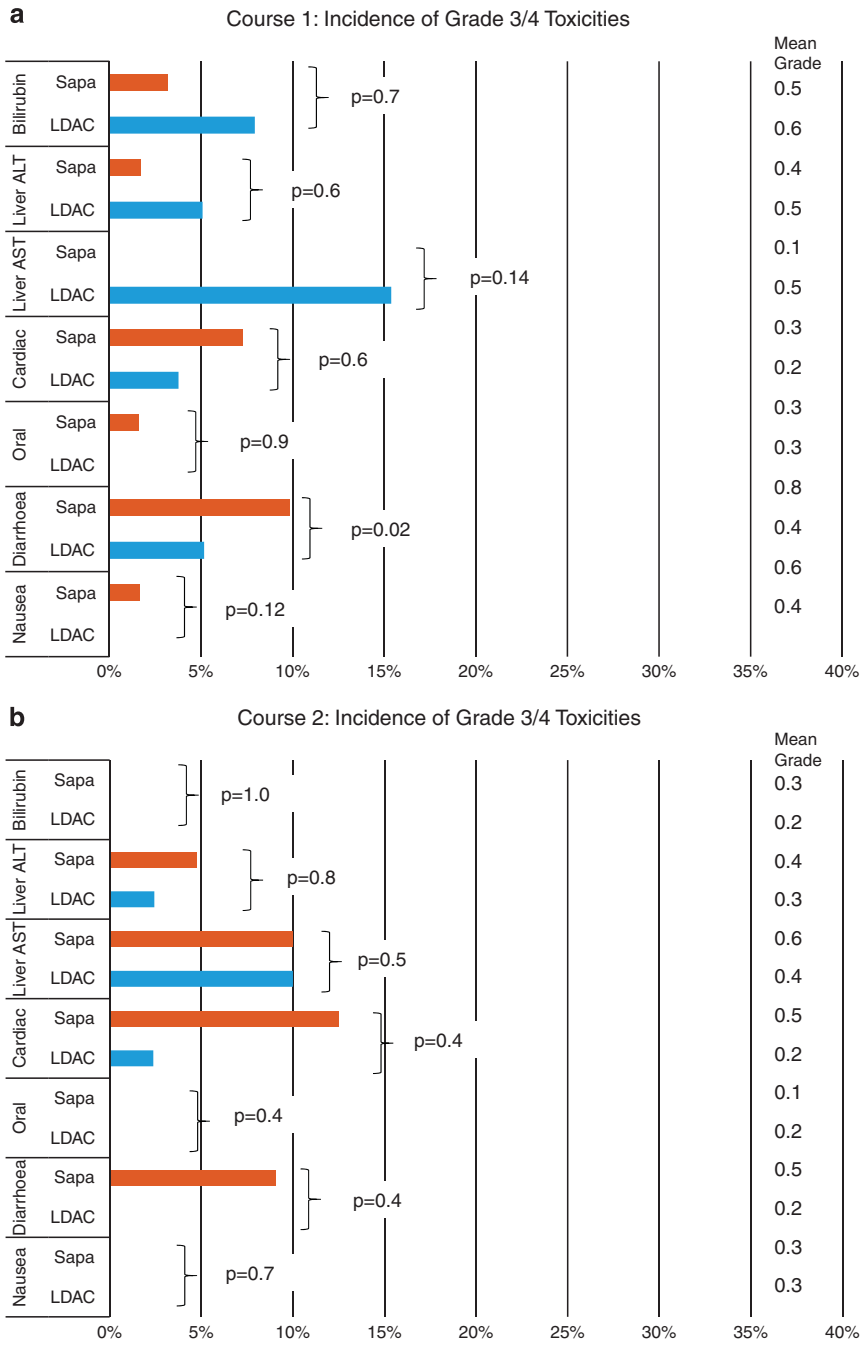

Figure 2. Grade 3/4 toxicities by course, with mean grade and test for differences using the Wilcoxon rank-sum test. The mean grade is the mean of all toxicity grades reported (NCI CTC grades 0–4); additionally the rate of grade 3/4 toxicity is presented graphically. (**a**) Course 1; (**b**) Course 2.

LDAC in various schedules has been used for many years,[25,26] but in our AML14 trial we established that it was superior to supportive care with no evidence for increased toxicity.[27] The survival benefit appeared to be limited to patients who entered CR (~15–20%). Since that trial, it has been the comparator to beat in six completed randomised attempts to improve the outcome for this patient group using our 'pick a winner' design. This design was based on our observation that improvement in survival was associated with achievement of CR, and therefore CR served as a useful surrogate for early assessment of a likely survival benefit. However, this assumption turned out not to be the case in two previous trials where both clofarabine and gemtuzumab ozogamicin combined with LDAC were able to double the remission rate but did not improve OS.[4,28] The requirement to improve the remission rate in order to improve survival has been questioned by the experience of demethylation agents. However, in randomised data so far demethylation agents have not shown significantly superior survival to LDAC given b.i.d. for 10 days.[6–8] Owing to insufficient numbers in the azacitidine trial with 20–30% blasts, the survival benefit was not confirmed in the LDAC subset, but the overall benefit seen was delivered by the comparison with best supportive care.[6] In the recently reported trial in AML with >30% blasts, significant survival was only apparent in the best supportive care comparison and was not significant vs LDAC.[7]

Table 3. Resource usage during courses 1 and 2

Toxicity	*LDAC*	*Sapacitabine*	*P-value*
Course 1			
Mean blood units	5.6	6.7	0.10
Mean platelet units	4.5	4.3	0.9
Mean days antibiotics	5.0	8.8	0.03
Mean day visits to hospital	4.5	6.0	0.13
Mean nights in hospital	10.8	12.4	0.3
Course 2			
Mean blood units	4.0	4.4	0.4
Mean platelet units	2.0	3.0	0.3
Mean days antibiotics	2.6	4.2	0.17
Mean day visits to hospital	4.5	6.6	0.05
Mean nights in hospital	6.3	7.4	0.8

Abbreviation: LDAC, low-dose ara-C.

In the decitabine trial the LDAC was given only once per day, which delivered a low CR rate.[8] In any case there is an urgent need for better treatments.

The Pick a Winner Programme[15] was devised to screen for new treatments that could make a useful clinical impact. The principle behind trials of this type is that there should be a reliable surrogate for survival, that event (remission or death) should be frequent and should occur early. Our initial experience comparing LDAC against best supportive care suggested that achievement of CR is closely correlated with clinical benefit. Subsequent experience has indicated that this alone is insufficient. Whereas an inadequate CR rate is unlikely to produce benefit for most drugs, a superior CR rate is not a guarantee of survival benefit. As explained in the methods section the DEMC's remit is to advise on the likely chance of benefit and whether appropriate to recommend continuation of the trial.

Sapacitabine is one of several novel nucleoside analogues for which there were encouraging data in older predominantly untreated but

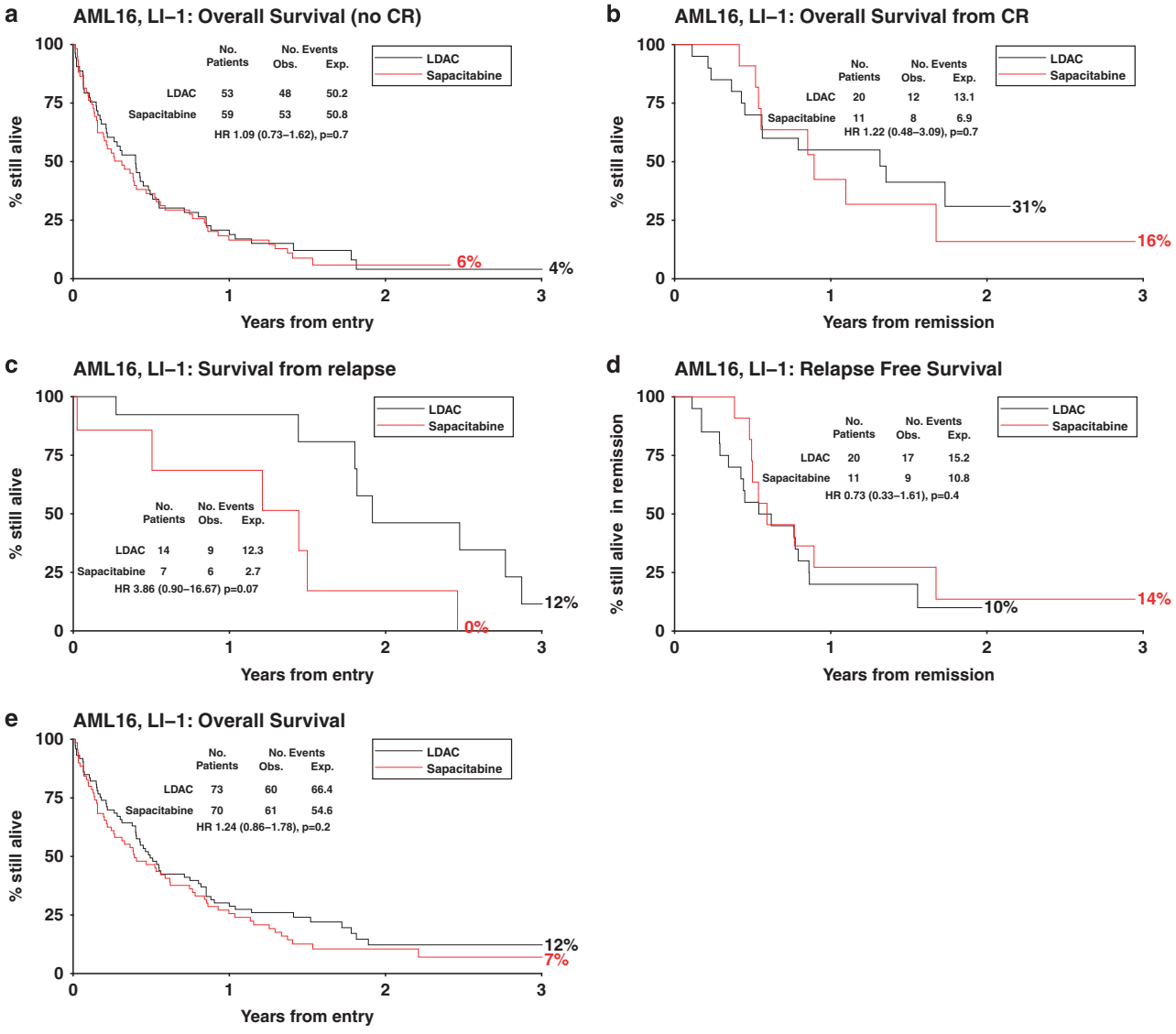

Figure 3. Outcomes for patients. (**a**) Survival for patients not achieving CR/CRi; (**b**) survival from CR/CRi; (**c**) survival from relapse; (**d**) relapse-free survival; (**e**) overall survival.

also relapsed patients to justify assessment as a first-line option. These studies, conducted by the MD Anderson Group, suggested that 400 mg b.i.d. for 3 days in two consecutive weeks every 3–4 weeks was the better schedule with a 60-day mortality of 26% and 1-year survival of 27%. The present prospective study in unselected older patients reproduces these results albeit with a different dosing schedule. We chose, following discussion with those familiar with the drug, a schedule of 300 mg b.i.d. for 3 days in two consecutive weeks. The conclusion of this randomised comparison is that, based on the efficacy and toxicity data, sapacitabine, as used here, and LDAC do not give different outcomes, although the oral option provided by sapacitabine could be considered an advantage for older patients, although we did observe a general trend for increased-grade toxicity, particularly diahorroea. Our preclinical data suggest that at least in some cases there is synergy with Ara-C. This may suggest that sapacitabine in combination could be more effective. This is currently being tested in a company-sponsored study alternating sapacitabine with decitibine in this older AML population.[29]

CONFLICT OF INTEREST

AKB has acted on a data monitoring committee for Cyclacel Ltd. The remaining authors declare no conflict of interest.

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REFERENCES

1 Burnett AK, Hills RK, Hunter A, Milligan D, Kell J, Wheatley K *et al.* The addition of arsenic trioxide to low-dose Ara-C in older patients with AML does not improve outcome. *Leukemia* 2011; **25**: 1122–1127.

2 Kantarjian HM, Erba HP, Claxton D, Arellano M, Lyons RM, Kovascovics T *et al.* Phase II study of clofarabine monotherapy in previously untreated older adults with acute myeloid leukemia and unfavorable prognostic factors. *J Clin Oncol* 2010; **28**: 549–555.

3 Burnett AK, Russell NH, Kell J, Dennis M, Milligan D, Paolini S *et al.* European development of clofarabine as treatment for older patients with acute myeloid leukemia not considered unsuitable for intensive chemotherapy. *J Clin Oncol* 2010; **28**: 2389–2395.

4 Burnett AK, Russell NH, Hunter AE, Milligan D, Knapper S, Wheatley K *et al.* Clofarabine doubles the response rate in older patients with acute myeloid leukemia but does not improve survival. *Blood* 2013; **122**: 1384–1394.

5 Burnett AK, Russell NH, Culligan D, Cavanagh J, Kell J, Wheatley K *et al.* The addition of the farnesyl transferase inhibitor, tipifarnib, to low dose cytarabine does not improve outcome for older patients with AML. *Br J Haematol* 2012; **158**: 519–522.

6 Fenaux P, Mufti GJ, Hellstrom-Liindberg E, Santini V, Gattermann N, Germing U *et al.* Azacytidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. *J Clin Oncol* 2010; **28**: 562–569.

7 Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH *et al.* Results of a Phase 3, Multicenter, Randomised, Open-label Study of Azacitidine (AZA) vs. conventional Care Regimens (CCR) in Older Patients with Newly Diagnosed Acute Myeloid Leukaemia (AML). *Haematologica* 2014; **99**(s1): 788 (abstract LB2433).

8 Kantarjian HM, Thomas XG, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J *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* 2012; **30** (21): 2670–2677.

9 Matsuda J, Nakajima Y, Azuma A, Tanaka M, Sasaki T. Nucleosides and nucleotides: 100. 2′-*C*-cyano-2′-deoxy-1-β-arabinofuranosylcytosine (CNDAC): Design of a potential mechanism-based DNA-strand-breaking antineoplastic nucleoside. *J Med Chem* 1991; **34**: 2917–2919.

10 Azuma A, Huang P, Matsuda A, Plunkett W. 2′-C-cyano-2-deoxy-β-D- arabinopentafuranosyl cytosine: a novel anticancer nucleoside analog that causes both DNA strand breaks and G2 arrest. *Mol Pharmacol* 2001; **59**: 725–731.

11 Serova M, Galmarini CM, Ghoul A, Benhadji K, Green SR, Chiao J *et al.* Antiproliferative effects of sapacitabine (CYC682), a novel2'-deoxycytidine-derivative, in human cancer cells. *Br J Cancer* 2007; **97**: 628–636.

12 Katz MH, Bouvet M, Takimoto S, Spivack D, Moossa AR, Hoffman RM. Selective antimetastatic activity of cytosine analog CS-682 in a red fluorescent protein orthotopic model of pancreatic cancer. *Cancer Res* 2003; **63**: 5521–5525.

13 Kantarjian H, Garcia-Manero G, O'Brien S, Faderl S, Ravandi F, Westwood R *et al.* Phase I clinical and pharmacokinetic study of oral sapacitabine in patients with acute leukemia and myelodysplastic syndrome. *J Clin Oncol* 2010; **28**: 285–291.

14 Kantarjian H, Faderl S, Garcia-Manero G, Luger S, Venugopal P, Maness L *et al.* Oral sapacitabine for the treatment of acute myeloid leukaemia in elderly patients: a randomised phase 2 study. *Lancet Oncol* 2012; **13**: 1096–1104.

15 Hills RK, Burnett AK. Applicability of a 'Pick a Winner' trial design to acute myeloid leukemia. *Blood* 2011; **118**: 2389–2394.

16 Sorror ML, Giralt S, Sandmaier BM, de Lima M, Shahjahan M, Maloney DG *et al.* Hematopoietic cell transplantation-specific comorbidity index as an outcome predictor for patients with acute myeloid leukemia in first remission: combined FHCRC and MDACC experiences. *Blood* 2007; **110**: 4606–4613.

17 Wheatley K, Brookes CL, Howman AJ, Goldstone AH, Milligan DW, Prentice AG *et al.* Prognostic factor analysis of the survival of elderly patients with AML in the MRC AML11 and LRF AML14 trials. *Br J Haematol* 2009; **145**: 598–605.

18 Cheson BD, Bennett JM, Kopecky KJ, Büchner T, Willman CL, Estey EH *et al.* Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol* 2003; **21**: 4642–4649.

19 Kantarjian H, O'Brien S, Cortes J, Giles F, Faderl S, Jabbour E *et al.* Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. *Cancer* 2006; **106**: 1090–1098.

20 Appelbaum FR, Gundacker H, Head DR, Slovak ML, Willman CL, Godwin JE *et al.* Age and acute myeloid leukemia. *Blood* 2006; **107**: 3481–3485.

21 Kantarjian H, Ravandi F, O'Brien S, Cortes J, Faderl S, Garcia-Manero G *et al.* Intensive chemotherapy does not benefit most older patients (age 70 years or older) with acute myeloid leukemia. *Blood* 2010; **116**: 4422–4429.

22 Burnett AK, Milligan D, Goldstone A, Prentice A, McMullin MF, Dennis M *et al.* The impact of dose escalation and resistance modulation in older patients with acute myeloid leukaemia and high risk myelodysplastic syndrome: the results of the LRF AML14 trial. *Br J Haematol* 2009; **145**: 318–332.

23 Krug U, Rollig C, Koschmieder A, Heinecke A, Sauerland MC, Schaich M *et al.* Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: a web-based application for prediction of outcomes. *Lancet* 2010; **376**: 2000–2008.

24 Juliusson G, Billstrom R, Gruber A, Hellström-Lindberg E, Höglunds M, Karlsson K *et al.* Attitude towards remission induction for elderly patients with acute myeloid leukemia influences survival. *Leukemia* 2006; **20**: 42–47.
25 Cheson BD, Japerse DM, Simon R, Friedman MA. A critical appraisal of low-dose cytosine arabinoside in patients with acute non-lymphocytic leukemia and myelodysplastic syndromes. *J Clin Oncol* **4**: 1857–18641986.
26 Tilly H, Castaigne S, Bordessoule D, Casassus P, Le Prisé PY, Tertian G *et al.* Low-dose cytarabine versus intensive chemotherapy in the treatment of acute nonlymphocytic leukemia in the elderly. *J Clin Oncol* 1990; **8**: 272–279.
27 Burnett AK, Milligan D, Prentice AG, Goldstone AH, McMullin MF, Hills RK *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* 2007; **109**: 1114–1124.
28 Burnett AK, Hills RK, Hunter AE, Milligan D, Kell WJ, Wheatley K *et al.* The addition of gemtuzumab ozogamicin to low-dose Ara-C improves remission rate but does not significantly prolong survival in older patients with acute myeloid leukaemia: results from the LRF AML14 and NCRI AML16 pick-a-winner comparison. *Leukemia* 2013; **27**: 75–81.
29 Ravandi F, Faderl S, Cortes J, Garcia-Manero G, Jabbour E, Boone PA *et al.* Phase I/II study of Sapacitabine and Decitabine administered sequentially in elderly patients with newly diagnosed AML. Abstract #81934. ASCO Annual Meeting 2011.

Supplementary Information accompanies this paper on the Leukemia website (http://www.nature.com/leu)