Oral sapacitabine for the treatment of acute myeloid leukaemia in elderly patients: a randomised phase 2 study

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Summary

Background Available treatments for acute myeloid leukaemia (AML) have limited durable activity and unsatisfactory safety profiles in most elderly patients. We assessed the efficacy and toxicity of sapacitabine, a novel oral cytosine nucleoside analogue, in elderly patients with AML.

Methods In this randomised, phase 2 study, we recruited patients with AML who were either treatment naive or at first relapse and who were aged 70 years or older from 12 centres in the USA. We used a computer-generated randomisation sequence to randomly allocate eligible patients to receive one of three schedules of oral sapacitabine (1:1:1; stratified by a history of AML treatment): 200 mg twice a day for 7 days (group A); 300 mg twice a day for 7 days (group B); and 400 mg twice a day for 3 days each week for 2 weeks (group C). All schedules were given in 28 day cycles. To confirm the safety and tolerability of dosing schedules, after 20 patients had been treated in a group we enrolled an expanded cohort of 20–25 patients to that group if at least four patients had achieved complete remission or complete remission with incomplete blood count recovery, and if the 30 day death rate was 20% or less. Our primary endpoint was 1-year overall survival, analysed by intention-to-treat (ie, patients who have received at least one dose of sapacitabine) in those patients who had been randomly allocated to treatment. This trial is registered with ClinicalTrials.gov, number NCT00590187.

Results Between Dec 27, 2007, and April 21, 2009, we enrolled 105 patients: 86 patients were previously untreated and 19 were at first relapse. Of the 60 patients randomly allocated to treatment, 1-year overall survival was 35% (95% CI 16–59) in group A, 10% (2–33) in group B, and 30% (13–54) in group C. 14 (13%) of 105 patients died within 30 days and 27 (26%) died within 60 days. The most common grade 3–4 adverse events were anaemia (eight of 40 patients in group A, 12 of 20 patients in group B, and 15 of 45 patients in group C), neutropenia (14 in group A, 10 in group B, 11 in group C), thrombocytopenia (24 in group A, 12 in group B, and 22 in group C), febrile neutropenia (16 in group A, nine in group B, and 22 in group C), and pneumonia (seven in group A, five in group B, and 10 in group C). The most common grade 5 events were pneumonia (two in group A, one in group B, and three in group C) and sepsis (six in group A, three in group B, and one in group C). Seven deaths were thought to be probably or possibly related to sapacitabine treatment.

Interpretation Sapacitabine seems active and tolerable in elderly patients with AML. The 400 mg dose schedule had the best efficacy profile. Future investigations should aim to combine sapacitabine with other low-intensity therapies in elderly patients with AML.

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Introduction

Despite substantial progress in the treatment of acute myeloid leukaemia (AML), intensive chemotherapy has a cure rate of only 30–50%.[1,2] Intensive chemotherapy does not benefit most elderly patients with AML, because of poor tolerance to chemotherapy, high rates of treatment-related mortality (30–50%), and a high incidence of adverse cytogenetic abnormalities.[1–4] Despite 40–50% of patients achieving complete remission (CR), the median survival in elderly patients treated with intensive chemotherapy is only 4–6 months. Median survival has not changed in the past two decades despite variations in intensive chemotherapy regimens and improvements in supportive care measures.[3] Investigations have assessed low-intensity therapies with hypomethylating drugs (decitabine, azacitidine) and other agents (low-dose cytarabine, gemtuzumab ozogamicin, clofarabine).[5–10] The development of novel drugs with new mechanisms of action, improved anti-leukaemic activity, and more favourable safety profiles is much needed.

Nucleoside analogues are a major class of antitumour cytotoxic agents, several of which are effective against leukaemia (cladribine, clofarabine, cytarabine, azacitidine, decitabine). Oral sapacitabine, 1-(2-C-cyano-2-deoxy-β-D-arabino-pentafuranosyl)-N⁴-palmitoylcytosine (also known as CYC682, CS-682) is a rationally designed analogue of cytarabine with a unique mechanism of action.[11] After oral administration, sapacitabine is converted to 2-C-cyano-2-deoxy-1-β(-D-arabino-pentafuranosyl) cytosine (CNDAC). After phos-

phorylation to the triphosphate form and incorporation into DNA, replication is not inhibited at cytotoxic concentrations (by contrast with cytarabine and clofarabine). Instead, after further polymerisation, the strong electrophilic properties of the cyano group of CNDAC causes a rearrangement of the nucleotide to a form without 3′-hydroxyl moiety.[12,13] This rearrangement results in a single-strand DNA break that is repaired to only a small extent. On a subsequent round of DNA replication, unrepaired single-strand DNA breaks are converted to double-strand breaks, causing cell death.[14,15]

Findings from a phase 1 study of oral sapacitabine given twice daily for 7 days or twice daily for 3 days every week for 2 weeks, in 3–4 week cycles, showed that sapacitabine was safe and had activity in patients with AML. The recommended phase 2 dose schedules were 325 mg twice daily for 7 days and 425 mg twice daily for 3 days, on days 1–3 and 8–10 of a 21–28 day cycle. Dose-limiting toxicities were mainly gastrointestinal. Of 47 patients treated for refractory-relapsed AML, 13 (28%) responded to treatment, including four who had complete remission.[16]

For the **ID-net randomisation service** see http://www.iddi.com

In this multicenter, phase 2, randomised study, we investigated three dosing schedules of oral sapacitabine in elderly patients with previously untreated or relapsed AML.

Methods

Study design and participants

For this multi-institutional, randomised phase 2 study, we recruited patients aged 70 years or older with AML from 12 medical centres in the USA, who were either previously untreated or at first relapse. Other eligibility criteria included: an Eastern Cooperative Oncology Group (ECOG) performance score of 0–2; adequate hepatic function (bilirubin <1·5 times the upper limit of normal [ULN] and alanine aminotransferase [ALT] <2·5 times the ULN or <5 times the ULN if hepatic leukaemic involvement was suspected); adequate renal function (creatinine concentrations ≤1·5 times the ULN); no previous chemotherapy for AML, radiation therapy, or investigational therapies for at least 2 weeks, with recovery from clinically important toxicities of these previous treatments. Patients with white blood cell counts 50×10^9 per L or higher were allowed to receive hydroxyurea for cytoreduction before starting treatment with sapacitabine. Exclusion criteria were: the presence of CNS disease, uncontrolled concurrent illnesses including active infections, active cancers, symptomatic congestive heart failure, unstable angina, cardiac arrhythmias, or inability to fully comply with the study protocol (eg, psychiatric illnesses or social situations).

Patients provided written informed consent in accordance with institutional guidelines at every participating centre and the ethical principles of the Declaration of Helsinki.

Randomisation and masking

Randomisation was done by the International Drug Development Institute (IDDI, Louvain-la-Neuve, Belgium [which was independent from the study]) with a fully validated interactive online randomisation service (ID-net). Dynamic randomisation, with a minimisation probability of 80%, was used to allocate patients. Patients were stratified by history of previous treatment (previously treated *vs* previously untreated) and were allocated to treatment in a 1:1:1 ratio). This was an open-label study so the investigators and patients were not masked to treatment.

Procedures

The three dose regimens were as follows: 200 mg twice a day for 7 days (group A); 300 mg twice a day for 7 days (group B); and 400 mg twice a day for 3 days each week for 2 weeks (group C). Courses of therapy were repeated every 28 days. Patients did not start their next cycle of treatment until any clinically significant or drug-related non-haematological toxicities had resolved to grade 0–1 or baseline. After recovery from a grade 3–4 drug-related

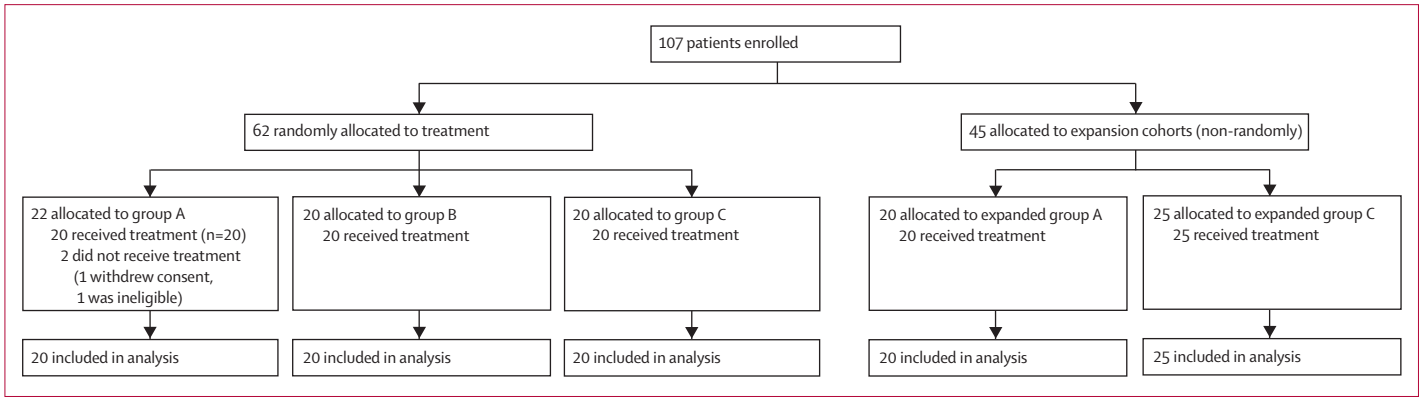

Figure 1: **Trial profile**
The randomisation phase was kept open until 20 patients in each group had received treatment. Five patients had already signed consent forms and been screened for study inclusion when the closure of expanded group C was announced (on enrolment of 20 patients)—these five patients were allowed to go into extended group C. Group A received 200 mg twice a day for 7 days. Group B received 300 mg twice a day for 7 days. Group C received 400 mg twice a day for 3 days each week for 2 weeks. All schedules were given for 28 day cycles.

non-haematological adverse event, a patient's twice-daily dose was reduced by 50 mg. Dose reductions for grade 2 toxicities were allowed for frail patients (patients judged to be frail on the basis of fulfilment of at least three of the following criteria: unintentional weight loss of 4·5 kg or more in a year, general feeling of exhaustion, weakness as measured by grip strength, slow walking speed, and low levels of physical activity).

Dose reductions for haematological toxicities were guided by findings from bone marrow biopsies, aspirates, or both (eg, percentage of blast cells), time to absolute neutrophil count, and platelet count recovery. If a patient's bone marrow blast cells decreased by 25% or more from baseline but remained more than 5% and there was a delay in recovery of blood counts to the best level on study beyond day 42, we reduced their twice-daily dose by 50 mg. If bone marrow contained 5% or fewer than 5% blast cells, a patient's twice-daily dose was reduced by 100 mg for persistent cytopenias as described above. For patients who were assigned to group A and tolerated treatment well, a dose escalation of up to 300 mg twice daily for 7 days was allowed. Patients could continue treatment indefinitely as long as there was no evidence of clinically significant AML progression. Prophylactic use of antibiotics and therapeutic use of growth factors were allowed according to institutional guidelines. Prophylactic use of haemopoietic growth factors was not allowed.

To assess response to treatment and possible toxicities, bone marrow biopsy, aspirate, or both were taken at baseline, before starting the second treatment cycle, and as indicated thereafter. Complete remission (CR) was defined as normalisation of blood and bone marrow with 5% or fewer blast cells, independence of transfusions, a granulocyte count of 10^9 per L or greater, and a platelet count of 100×10^9 per L or greater.[17,18] We defined a partial remission (PR) much like we defined CR, but with at least 50% decrease in bone marrow blast cells and to a level of 6% or more. Complete remission with incomplete platelet recovery (CRp) was defined much like CR but without platelet count recovery to 100×10^9 per L or greater. Complete remission with incomplete blood count recovery (CRi) or marrow CR was defined much like CR but without granulocyte or platelet count recovery. We defined haematological improvement (HI) according to the International Working Group criteria.[18]

Statistical analysis

The primary objective was the assessment of 1-year overall survival in randomised patients. Secondary objectives were to assess clinical outcome in terms of CR, CRp, PR, CRi, or HI, and corresponding durations, transfusion requirements, and number of days spent in hospital.

Initially, we enrolled cohorts of 20 patients in each treatment group. To confirm the safety and tolerability of dosing schedules, after 20 patients had been treated we enrolled an expanded cohort of 20–25 patients to groups if at least four patients had CR or CRi, and if the 30 day death rate in that group was 20% or less. Because time to response varies from two cycles to nine cycles, we could not expand all promising dosing schedules by random assignment.

All patients who received at least one dose of sapacitabine and who had been randomly assigned to treatment were included in the primary analysis of overall survival. Overall survival was measured from the date of randomisation (survival was measured from the date of registration in the expanded cohorts). We estimated time-to-event endpoints such as overall survival and response durations by the Kaplan-Meier method.

We used a Bayesian continuous futility monitoring rule, for each dose schedule separately, based on the rate of CR plus CRi as follows: the enrolment to a dose schedule would be stopped if there was less than a 5% chance that the rate of CR plus CRi was greater than 25% from the

	Randomised group A (n=20)	Expanded group A (n=20)	Randomised group B (n=20)	Randomised group C (n=20)	Expanded group C (n=25)
Age					
70–79 years	11 (55%)	14 (70%)	14 (70%)	14 (70%)	21 (84%)
80 years or older	9 (45%)	6 (30%)	6 (30%)	6 (30%)	4 (16%)
Women	9 (45%)	8 (40%)	7 (35%)	7 (35%)	13 (52%)
ECOG performance status					
0–1	17 (85%)	15 (75%)	16 (80%)	18 (90%)	22 (88%)
2	3 (15%)	5 (25%)	4 (20%)	2 (10%)	3 (12%)
Untreated	16 (80%)	19 (95%)	17 (85%)	15 (75%)	19 (76%)
De novo	9	11	3	7	8
Preceded by MDS/MPN	6/0	6/1	11/2	6/2	9/1
Treatment-related	1	1	0	0	1
Other	0	0	1	0	0
First relapsed	4 (20%)	1 (5%)	3 (15%)	5 (25%)	6 (24%)
De novo	3	1	2	5	4
Preceded by MDS/MPN	1/0	0/0	0/0	0/0	1/0
Treatment-related	0	0	0	0	1
Other	0	0	1	0	0
Complete remission duration before enrolment					
<6 months	1	1	1	1	1
≥6 months	3	0	2	4	4
Unknown	0	0	0	0	1
Cytogenetics risk					
Favourable	0	0	0	0	1 (5%)
Intermediate	13 (65%)	9 (45%)	6 (30%)	10 (50%)	13 (52%)
Unfavourable	6 (30%)	8 (40%)	10 (50%)	8 (40%)	9 (45%)
Unknown	1 (5%)	1 (5%)	1 (5%)	1 (5%)	0
Missing or not assessable	0	2 (10%)	3 (15%)	1 (5%)	2 (8%)
Bone marrow blasts ≥50%	8 (40%)	7 (5%)	7 (35%)	11 (55%)	8 (32%)

Data are n or n (%). Group A received 200 mg twice a day for 7 days. Group B received 300 mg twice a day for 7 days. Group C received 400 mg twice a day for 3 days each week for 2 weeks. ECOG=Eastern Cooperative Oncology Group. MDS=myelodysplastic syndromes. MPN=myeloproliferative neoplasia.

Table 1: **Baseline characteristics**

data obtained from patients who had been treated on that dose schedule. We used a selection design to choose the better dosing schedule on the basis of 1-year overall survival if all three dosing schedules were shown to have activity based on the occurrence of CR plus CRi. If the better dosing schedule had a true 1-year overall survival of 45% and the worst dosing schedule a true 1 year overall survival of 30%, the trial had better than 80% probability to choose the correct dosing schedule with 20 patients treated with each dosing schedule. This trial was not sufficiently powered to compare the three dosing regimens for 1-year overall survival.

We used the following prognostic factors in univariate and multivariable analyses to assess the effect of each regimen on 30 day mortality, 60 day mortality, and 1 year survival: age (70–74 years *vs* 75–79 years *vs* 80 years or older), ECOG score (0–1 *vs* 2), peripheral white blood cell counts ($<10\times10^9$ per L *vs* $\geq10\times10^9$ per L), platelet counts ($<50\times10^9$ per L *vs* $\geq50\times10^9$ per L), creatinine concentration (≤ULN *vs* >ULN), bone marrow blast cells (<50% *vs* ≥50%), AML type (de novo *vs* other), previous treatment (newly diagnosed *vs* first relapsed), treatment group (group A *vs* group B *vs* group C), cytogenetic risk by Southwest Oncology Group (SWOG) classification (unfavourable *vs* intermediate, unknown, or missing), and chromosomal abnormalities (complex [three or more abnormalities] *vs* non-complex [one or two abnormalities] *vs* others). We used logistic models for 30 day mortality and 60 day mortality and a Cox

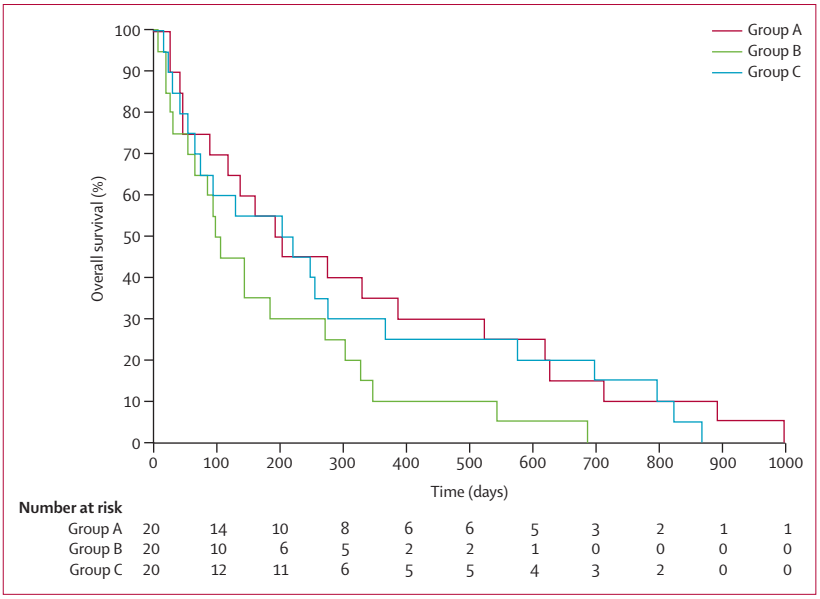

Figure 2: **Kaplan-Meier plot of overall survival, by treatment group**

	Randomised group A (n=20)	Expanded group A (n=20)	Randomised group B (n=20)	Randomised group C (n=20)	Expanded group C (n=25)
1-year overall survival (% [95% CI])	35% (16–59)	10% (2–33)	10% (2–33)	30% (13–54)	24% (10–46)
Median survival in days (95% CI)	197 (48–385)	151 (39–225)	102 (32–186)	213 (56–277)	159 (76–236)
Number of patients with an overall response (% [95% CI])	9 (45% [24–68])	6 (30% [13–54])	6 (30% [13–54])	9 (45% [24–68])	6 (24% [10–46])
CR (n)	2	2	1	5	2
CRp (n)	0	0	1	0	0
CRi (n)	1	1	0	1	0
PR (n)	0	1	1	0	1
HI (n)	6*	2	3	3	3

Group A received 200 mg twice a day for 7 days. Group B received 300 mg twice a day for 7 days. Group C received 400 mg twice a day for 3 days each week for 2 weeks. CR=complete remission. CRp=CR with incomplete platelet count recovery. CRi=CR with incomplete blood count recovery. PR=partial remission. HI=haematological improvement. *one patient achieved CRi in September, 2008, and major HI in platelets in October, 2008.

Table 2: **Survival and response outcomes**

	Randomised group A (n=20)	Expanded group A (n=20)	Randomised group B (n=20)	Randomised group C (n=20)	Expanded group C (n=25)	Total (n=105)
Number of deaths in first 30 days	2 (10% [2–33])	3 (15% [4–39])	4 (20% [7–44])	2 (10% [2–33])	3 (12% [3–32])	14 (13% [8–22])
Number of deaths in the first 60 days	5 (25% [10–49])	5 (25% [10–49])	6 (30% [13–54])	5 (25% [10–49])	6 (24% [10–46])	27 (26% [18–35])
Median number of treatment cycles (range)	3 (1 to >23)	3 (1 to >22)	3 (1 to 9)	3 (1 to 23)	2 (1 to >17)	3 (1 to >23)
Number of patients treated with four or more cycles	8	4	8	7	6	33
Number of dose reductions	3 (15% [4–39])	3 (15% [4–39])	9 (45% [24–68])	8 (40% [20–64])	13 (52% [32–72])	36 (34% [25–44])

Data are n (% [95% CI]), unless otherwise stated. Group A received 200 mg twice a day for 7 days. Group B received 300 mg twice a day for 7 days. Group C received 400 mg twice a day for 3 days each week for 2 weeks.

Table 3: **Safety of sapacitabine schedules and treatment delivery**

proportional hazard model for 1-year overall survival. We used a two-sided p value of less than 0·1 to select factors to be included in the multivariate analyses. A two-sided p value of less than 0·05 was thought to be significant. We used SAS (version 9.2), JMP (version 8.0.1), and VassarStat for all statistical analyses.

The trial is registered with ClinicalTrials.gov, number NCT00590187.

Role of the funding source

The sponsor of the study, HK, and WP designed the trial. HK, SL, PV, LM, MW, SC, WS, DC, SLG, MA, SAS, KS, GS had access to raw data for their sites—the study sponsor had full access to all raw data. The sponsor collected, analysed, and interpreted the data in collaboration with HK, SL, PV, LM, MW, SC, WS, DC, SLG, MA, SAS, KS, and GS. The corresponding author (HK) had full access to the data and the final responsibility for the decision to submit for publication.

Results

Between Dec 27, 2007, and April 21, 2009, we enrolled 107 patients, of whom two did not receive treatment (figure 1). The median length of follow-up was 143 weeks

	Group A (n=40)			Group B (n=20)			Group C (n=45)			p value*
	Grade 1–2	Grade 3–4	Grade 5	Grade 1–2	Grade 3–4	Grade 5	Grade 1–2	Grade 3–4	Grade 5	
Anaemia	4	8	0	0	12	0	4	15	0	0·08
Febrile neutropenia	0	16	0	0	9	0	0	22	0	0·01
Neutropenia	0	14	0	0	10	0	2	11	0	0·41
Thrombocytopenia	0	24	0	0	12	0	0	22	0	0·02
Atrial fibrillation	2	2	0	2	2	0	2	4	0	0·96
Abdominal pain	6	4	0	3	0	0	1	2	0	0·05
Constipation	10	1	0	8	1	0	11	0	0	0·87
Diarrhoea	23	2	0	11	2	0	17	3	0	0·07
Nausea	16	1	0	6	0	0	23	2	0	0·001
Stomatitis	4	0	0	2	0	0	7	0	0	0·23
Vomiting	12	0	0	5	0	0	11	1	0	0·14
Fatigue	19	3	0	10	1	0	13	4	0	0·11
Peripheral oedema	5	1	0	8	0	0	15	2	0	0·03
Hyperbilirubinaemia	1	1	0	2	3	0	0	0	0	0·12
Fever	6	1	0	1	0	0	9	0	0	0·02
Bacteraemia	2	5	0	1	0	2	0	5	0	0·03
Cellulitis	3	3	0	0	3	0	3	5	0	0·38
Pneumonia	1	7	2	1	5	1	1	10	3	0·70
Sepsis	0	3	6	0	0	3	0	1	1	0·08
Anorexia	9	1	0	5	0	0	8	0	0	0·49
Weight decreased	3	0	0	4	0	0	3	1	0	0·99
Hypokalaemia	3	2	0	0	1	0	4	3	0	0·21
Arthralgia	7	1	0	0	0	0	5	1	0	0·02
Back pain	4	2	0	1	0	0	6	0	0	0·08
Musculoskeletal chest pain	1	1	0	0	0	0	6	2	0	0·006
Pain in extremity	7	0	0	1	0	0	8	0	0	0·03
Dizziness	7	0	0	3	0	0	10	0	0	0·126
Headache	7	0	0	0	0	0	6	3	0	0·002
Insomnia	4	1	0	1	0	0	7	0	0	0·08
Cough	9	0	0	3	0	0	6	0	0	0·19
Dyspnoea	15	2	0	2	0	0	10	2	0	0·001
Epistaxis	6	0	0	3	1	0	5	0	0	0·68
Ecchymosis	4	1	0	3	1	0	1	1	0	0·77
Petechiae	4	1	0	3	0	0	7	0	0	0·40
Alopecia	7	0	0	2	0	0	10	0	0	0·04
Rash	5	1	0	1	1	0	7	1	0	0·16
Hypotension	4	2	0	0	0	0	3	4	0	0·04

Group A received 200 mg twice a day for 7 days. Group B received 300 mg twice a day for 7 days. Group C received 400 mg twice a day for 3 days each week for 2 weeks.
*Fisher's Exact test.

Table 4: **Adverse events occurring in more than 15% of patients**

	Previously untreated (n=86)			First relapsed (n=19)			p value*
	Grade 1–2	Grade 3–4	Grade 5	Grade 1–2	Grade 3–4	Grade 5	
Anaemia	6	29	0	2	6	0	0·85
Febrile neutropenia	0	39	0	0	8	0	1
Neutropenia	2	29	0	0	6	0	1
Thrombocytopenia	0	48	0	0	10	0	0·80
Atrial fibrillation	5	5	0	1	3	0	0·31
Abdominal pain	11	5	0	1	1	0	0·87
Constipation	28	2	0	1	0	0	0·031
Diarrhoea	41	5	0	10	2	0	0·57
Nausea	35	3	0	10	0	0	0·7
Vomiting	22	1	0	6	0	0	0·66
Fatigue	33	6	0	9	2	0	0·58
Peripheral oedema	23	3	0	5	0	0	1
Fever	11	1	0	5	0	0	0·32
Candidiasis or oral candidiasis	8	0	0	5	1	0	0·01
Cellulitis	4	7	0	2	4	0	0·07
Pneumonia	2	19	5	1	3	1	0·78
Anorexia	19	1	0	3	0	0	0·80
Hypokalaemia	6	3	0	1	3	0	0·11
Hypophosphataemia	0	3	0	1	3	0	0·02
Arthralgia	9	1	0	3	0	0	0·55
Back pain	7	2	0	4	0	0	0·23
Muscle spasm	2	0	0	3	0	0	0·04
Musculoskeletal chest pain	3	3	0	4	0	0	0·03
Pain in extremity	14	0	0	2	0	0	0·73
Dizziness	15	0	0	5	0	0	0·35
Headache	12	2	0	1	1	0	0·39
Cough	16	0	0	2	0	0	0·52
Dyspnea	22	2	0	5	2	0	0·24
Epistaxis	12	1	0	2	0	0	1
Petechiae	10	0	0	4	0	0	0·28
Alopecia	15	0	0	4	0	0	0·74
Rash	12	1	0	2	0	0	1
Hypotension	6	4	0	1	2	0	0·52

*Fisher's exact test.

Table 5: **Adverse events occurring in more than 15% of patients (previously untreated *vs* first relapsed)**

(IQR 123–143). After assessment of the first 60 patients, we recorded favourable preliminary results in only group A and group C, and so expanded these two groups. We expanded group A first, expanding group C after 20 patients had been added to group A.

Baseline characteristics are shown in table 1. The median age of patients was 77 years (range 70–91). Baseline characteristics were much the same between the three initial cohorts, the main differences being that the proportion of patients with AML preceded by myelodysplastic syndromes (MDS) or myeloproliferative neoplasms (MPN) was higher in group B than it was in groups A and C. Baseline characteristics were also much wthe same between the two expanded groups. 50 patients (48%) had AML after MDS or MPN, or secondary to therapy for other primary cancers. Previous treatment for AML included cytarabine (13 patients), anthracycline or anthracenedione (11 patients), and hypomethylating agents (eight patients). In patients with newly diagnosed AML, unfavourable cytogenetics were present in 35 patients (41%).[19] 59 patients (56%) required transfusion of packed red blood cells, platelets, or both before study entry.

As of the data cutoff date of July 15, 2011, 101 patients had died: 39 in group A, 20 in group B, and 42 in group C. Among the original cohort of 60 patients who underwent randomisation, 1-year overall survival was 35% (95% CI 16–59) in group A, 10% (2–33) in group B, and 30% (13–54) in group C. Median overall survival was 197 days (95% CI 48–385) in group A, 102 days (32–186) in group B, and 213 days (56–277) in group C, respectively (figure 2). Median overall survival and 1-year overall survival in the expanded cohorts are shown in table 2.

Of all 105 patients, 36 patients had a treatment response (either CR, CRp, CRi, PR, or HI; table 2). 28 of these patients were previously untreated: nine had CR, one had CRp, three had CRi, two had PR, and 13 had HI. Of the eight patients who had a treatment response after first relapse, three had CR, one had PR, and four had HI. The median overall survival of the 12 patients who achieved CR was 525 days (95% CI 192–798). The median overall survival of the 24 patients achieving CRp, CRi, PR, or HI was 277 days (228–542). In the three initial cohorts, the median duration of CR or CRp was 197 days (95% CI 28–468) and the median duration of other responses was 70 days (14–77).

Of the 29 patients with de-novo AML who were randomly allocated to treatment, 1-year overall survival was 17% (95% CI 5–45) for the 12 patients in group A, 0% (0–43) for the five patients in group B, and 33% (14–61) for the 12 patients in group C. Of the 28 patients with AML preceded by MDS or MPN who were randomly allocated to treatment, 1-year overall survival was 57% (25–84) for the seven patients in group A, 8% (1–33) for the 13 patients in group B, and 25% (7–59) for the eight patients in group C. Of the 23 patients who survived 1 year or more, seven patients achieved CRs, two achieved PRs, seven achieved major HIs, four had stable disease (defined as on study for longer than 16 weeks without clinically detectable disease progression), and three did not achieve any response. The patient who received sapacitabine for the longest, who received a total of 30 cycles, achieved a PR. These subgroup analyses should be considered exploratory and hypothesis generating.

Of the 60 patients in the initial cohort, the mean number of packed red blood cells transfused per patient per month on study after enrolment was much the same in group A (4·30 units per patient) and group C (4·93 units per patient) but was higher in group B (7·42 units per patient). More platelet transfusions were needed in group B (17·86 units per patient per

month) compared with the number needed in group A (5·67 units per patient per month) and group C (12·47 units per patient per month). The percentage of days spent in hospital while in the study was much the same in group A (397 of 4319 days [9%]) and group C (306 of 4201 days [7%]) but was higher in group B (333 of 2158 days [15%]).

For the 45 patients in the expanded cohort, the mean number of packed red blood cells transfused per patient per month was 4·84 units per patient in expanded group A and 4·93 units per patient in expanded group C. The mean number of platelets transfused was 4·07 units per patient in expanded group A and 5·38 units per patient in expanded group C; the percentage of days spent in hospital while on study was 16% (325 of 1980 days) and 10% (357 of 3594 days), respectively.

Overall, 14 patients (13%) died during the first 30 days of the study and 27 patients (26%) died within 60 days of study entry. There was no difference in mortality between groups A and C at either 30 days or 60 days; by contrast, mortality was higher in group B at both timepoints (table 3). The study site investigator regarded seven deaths to be probably or possibly related to sapacitabine: pneumonia (two in group C), sepsis (three in group A), cerebral haemorrhage (one in group B), and neutropenic colitis (one in group A).

The median numbers of cycles were much the same between treatment groups and the number of patients with sapacitabine dose reductions in subsequent cycles was higher in group B than it was in group C (table 3). The most common grade 3–4 adverse events were anaemia, neutropenia, thrombocytopenia, febrile neutropenia, and pneumonia (table 4). The most common serious adverse events were myelosuppression-related complications, with febrile neutropenia and pneumonia being the most frequent. The most common non-haematological adverse events were gastrointestinal (most of which [90%] were grade 1–2; table 4). Gastrointestinal symptoms were manageable and only 2% resulted in dose reduction. More patients in group A and B had bacteraemia compared with patients in group C, and two patients in group B died from bacteraemia. The toxicities in previously untreated patients were similar in number and type to those in the first relapsed patients (table 5). In total, ten patients died from sepsis: six in group A, three in group B, and one in group C. We recorded two cases of neutropenic colitis, one in group A (which resulted in death) and one in group B.

In multivariable analysis of prognostic factors associated with 30 day mortality, we identified a platelet count of 50×10^9 per L or less as an adverse factor; we detected no prognostic factors associated with 60 day mortality (table 6). The only independent adverse factors for 1-year overall survival were a platelet count of 50×10^9 per L or less and an unfavourable cytogenetic risk profile (table 6).

	Univariable analysis		Multivariable analysis	
	Effect size (95% CI)	p value	Effect size (95% CI)	p value
Adverse factors for 30 day mortality*				
ECOG score of 2	5·5 (1·6–18·7)	0·007	4·0 (0·9–17·3)	0·068
Platelet count <50×10⁹ per L	8·6 (1·8–40·7)	0·0067	7·5 (1·5–39·0)	0·0156
Creatinine >upper limit of normal	4·9 (1·5–16·7)	0·0103	4·1 (1·0–17·2)	0·057
Bone marrow blasts ≥50%	3·5 (1·1–11·3)	0·0375	2·9 (0·7–12·5)	0·164
Diagnosis of de novo AML	2·9 (0·9–10·0)	0·0882	1·9 (0·4–8·7)	0·385
Adverse factors for 60 day mortality*				
ECOG score of 2	3·2 (1·1–9·5)	0·0333	2·5 (0·8–8·2)	0·128
Platelet count <50×10⁹ per L	3·0 (1·2–7·5)	0·0206	2·6 (1·0–7·0)	0·054
Creatinine >upper limit of normal	3·8 (1·3–11·1)	0·0129	3·1 (1·0–9·7)	0·050
Bone marrow blasts ≥50%	2·7 (1·1–6·5)	0·0330	2·6 (1·0–6·8)	0·052
1 year overall survival†				
ECOG score of 2	1·7 (0·9–2·9)	0·0891	1·7 (0·9–3·1)	0·084
Peripheral white blood cell count ≥10×10⁹ per L	1·5 (1·0–2·3)	0·0767	1·3 (0·8–2·1)	0·264
Platelet count <50×10⁹ per L	2·6 (1·7–4·0)	<0·0001	2·4 (1·5–3·9)	<0·001
Creatinine >upper limit of normal	2·0 (1·2–3·5)	0·009	1·6 (0·9–2·8)	0·098
Unfavourable by SWOG cytogenetic risk	1·8 (1·1–2·7)	0·0122	1·6 (1·0–2·5)	0·044

ECOG=Eastern Cooperative Oncology Group. AML=acute myeloid leukaemia. SWOG=Southwest Oncology Group. *Effect size given as odds ratio. †Effect size given as hazard ratio.

Table 6: **Prognostic factors associated with 30 day mortality, 60 day mortality, and 1 year survival (n=105)**

Discussion

Our findings suggest that sapacitabine shows encouraging activity in elderly patients with AML. Toxicities were mostly myelosuppression-related, probably because patients with AML have compromised bone marrow before treatment and also due to the known myelosuppressive effect of sapacitabine. The major non-haematological toxicities were gastrointestinal, and were mostly mild to moderate in nature.

The 200 mg and 400 mg dose schedules had better 1-year overall survival than did the 300 mg group. However, 1-year overall survival in the 200 mg expanded cohort was low by comparison with the 400 mg expanded cohort, which was more consistent with that seen in the initial cohort (30%). Overall, therefore, the 400 mg dose schedule seems to have a better efficacy profile than the 200 mg and 300 mg dose schedules, both in terms of 1-year overall survival and in terms of more patients achieving a CR. However, all patients who achieved a CR in group C had their dose reduced because of myelosuppression, suggesting that a lower dose should be used if sapacitabine is to be combined with another myelosuppressive agent.

A limitation of the study is the small sample sizes, which did not allow formal statistical comparison between the three dose schedules. Because of the overall small sample size and the heterogeneity of the population of study participants, a larger randomised study is needed to substantiate the findings from this study.

Outcome for elderly patients with AML is poor. In clinical practice, a substantial proportion of older

Panel: Research in context

Systemic review

We convened an international panel of AML experts to review treatment options for elderly patients with AML. All experts reviewed published literature on randomized trials in AML and agreed that available treatments were not adequate and new safe and effective therapies are urgently needed.

Interpretation

Our findings suggests that improvement of survival in elderly patients with AML might be possible by controlling the disease with a low-intensity therapy that has a favourable safety profile rather than by achieving higher complete remission rates with intensive, toxic therapy. Sapacitabine in combination with decitabine, a low-intensity therapy, is being assessed in a large randomised phase 3 study with the primary efficacy endpoint of overall survival.

patients are not treated with intensive treatment by choice or because it is thought to be unsuitable. Unsuitable can mean that the patient is medically unfit and such treatment might curtail survival, or that the patient is medically fit but unlikely to benefit because of unfavourable disease features (eg, cytogenetics or secondary disease; panel).[20]

Targeted therapies against AML signalling pathways, such as FLT3 inhibitors, have yielded favourable results but their use is restricted to patients with the appropriate target.[21] Targeted therapies can be given alone, in combination with intensive chemotherapy (in younger patients), or with low-intensity therapy (in older patients). Hypomethylating agents have also shown encouraging results with low treatment-associated mortality and good survival, despite the low rate of objective CRs.[9,10] These findings suggest that survival in elderly patients with AML could be improved by controlling the disease with low-intensity therapies that have favourable safety profiles rather than by aiming for a higher proportion of patients to achieve CR with intensive, toxic therapy. A randomised study assessing decitabine versus low-dose cytarabine in patients aged 65 years or older with AML showed an improvement in median survival with decitabine despite only 18% of patients achieving CR.[9] Additional studies are ongoing with other adenosine nucleoside analogues, including clofarabine (NCT01041703). A Medical Research Council trial (ISRCTN40571019) is assessing low-dose clofarabine versus low-dose cytarabine in elderly patients with AML. If one or more such low-intensity therapies are shown to be active and safe, combined modality therapies could improve the outcome in this poor-prognosis group. Trials of combination regimens with clofarabine and low-dose cytarabine alternating with hypomethylating agents are ongoing.[22] A pilot study assessing sapacitabine 300 mg, orally, twice a day, for 3 days a week for 2 weeks in alternating cycles with decitabine has generated favourable safety and efficacy results.[23] The oral nature of sapacitabine allows multiple cycles to be given at home, offering a distinct advantage over intravenous drugs, which require frequent visits to hospital or a clinic. This advantage is important for elderly patients, for whom the treatment goal is to extend survival with a good quality of life. A randomised phase 3 study assessing sapacitabine administered by the 3 day schedule (at a 300 mg dose) in alternating cycles with decitabine versus decitabine alone is ongoing to establish the safety and efficacy of sapacitabine in the treatment of elderly patients with AML (NCT01303796).

Contributors

HK, JC, and WP had the idea for and designed the study. HK, SF, GG-M, SL, PV, LM, MW, SC, WS, DC, SLG, MA, SAS, KS, GS, and EJ provided of study material or recruited patients. HK, SL, PV, LM, MW, SC, WS, DC, SLG, MA, SAS, KS, GS, and JC analysed and interpreted data. HK lead the writing of the paper. All authors approved the final version of the paper.

Conflicts of interest

HK, GS, and MW received research grants from Cyclacel Ltd, who provides sapacitabine. JC is an employee of Cyclacel. The other authors declare that they have no conflicts of interest.

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