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ORIGINAL REPORT

Phase I Clinical and Pharmacokinetic Study of Oral Sapacitabine in Patients With Acute Leukemia and Myelodysplastic Syndrome

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ABSTRACT

Purpose
Sapacitabine is an oral deoxycytidine nucleoside analog with a unique mechanism of action that is different from cytarabine.

Patients and Methods
To define the dose-limiting toxicities (DLT) and maximum-tolerated dose (MTD) of sapacitabine given orally twice daily for 7 days every 3 to 4 weeks, or twice daily for 3 days for 2 weeks (days 1 through 3 and days 8 through 10) every 3 to 4 weeks, in refractory-relapse acute leukemia and myelodysplastic syndrome (MDS). A total of 47 patients were treated in the phase I study that used a classical 3 + 3 design. Sapacitabine was escalated from 75 to 375 mg twice daily for 7 days (n = 35) and from 375 to 475 mg twice daily for 3 days on days 1 through 3 and days 8 through 10.

Results
The DLTs with both schedules were gastrointestinal. The MTDs were 375 mg twice daily for 7 days and 425 mg twice daily for 3 days on days 1 through 3 and days 8 through 10. The recommended phase II single-agent dose schedules were 325 mg twice daily for 7 days and 425 mg twice daily for 3 days on days 1 through 3 and days 8 through 10. Responses were observed in 13 patients (28%); four were complete responses, and nine were marrow complete responses.

Conclusion
Sapacitabine is a new, safely administered, oral deoxycytidine analog that has encouraging activity in leukemia and MDS. Phase II studies are ongoing.

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INTRODUCTION

Despite recent progress in acute myeloid leukemia (AML), modern combination-chemotherapy regimens result in complete response (CR) rates of 40% to 70% and long-term event-free survival rates of only 20% to 50%, depending on patient ages, comorbid conditions, and leukemia karyotypes.[1,2] Similar results are noted in adult acute lymphocytic leukemia (ALL), for which long-term event-free survival rates are only 30% to 40%.[3,4] In myelodysplastic syndrome (MDS), several recent studies with azacitidine, decitabine, and lenalidomide have shown encouraging results.[5-7] However, the median survival remains short, in the range of 2 to 3 years. These findings indicate the need to discover new strategies that might improve the outcomes in leukemia and MDS. Nucleoside analogs represent a major group of antitumor cytotoxic agents. Several agents in this class have shown activity in leukemia and MDS. These include deoxyadenosine analogs, such as fludarabine, deoxycoformycin, chlorodeoxyadenosine, and clofarabine,[8,9] or cytosine nucleoside analogs, such as cytarabine,[1,2] azacitidine, and decitabine.

$2'$-C-Cyano-$2'$-deoxy-β-D-arabino-pentofuranosylcytosine (CNDAC) is a rationally designed analog of deoxycytidine with a unique mechanism of action.[10] On phosphorylation to the triphosphate and incorporation into DNA, replication is not inhibited at cytotoxic concentrations, unlike cytarabine, fludarabine, or clofarabine. Rather, after additional polymerization, the strong electrophilic properties of the cyano group cause a rearrangement of the nucleotide to a form that lacks a $3'$-hydroxyl moiety.[11,12] This results in a single-strand break that is repaired to only a small extent by the transcription-coupled nucleotide excision pathway.[13] On a subsequent round of DNA replication, unrepaired single-strand breaks are converted to double-strand breaks, which leads to cell death.[14]

During the discovery phase, many derivatives of CNDAC were studied. Sapacitabine (previously designated CS-682), an N4-palmitoyl derivative of CNDAC, was chosen for clinical development because of its broad range of antitumor activity in preclinical studies.[11] The palmitoyl side chain on CNDAC allows for improved oral absorption of sapacitabine and protects the N4 amino group from deamination, which is a major route of inactivation for this class of molecule.[11] After oral administration, sapacitabine is converted to CNDAC by amidases and esterases in the gastrointestinal tract, plasma, and liver, and it becomes bioavailable[15,16] at concentrations that reduce clonogenic survival of cells in vitro.[13]

CNDAC has shown positive preclinical activity in a broad spectrum of human tumor cells, including leukemic cell lines. The phase I studies of single-agent sapacitabine in solid tumors identified myelosuppression as the dose-limiting toxicity (DLT).[15,16] This is generally a favorable feature for agents that ultimately demonstrate activity in leukemia at three-fold to 20-fold of the maximum-tolerated doses (MTDs) observed in solid tumors. These findings, together with the oral bioavailability of sapacitabine, led to the interest in developing it for hematologic malignancies.

PATIENTS AND METHODS

Patient Eligibility

Adults with relapsed or refractory acute leukemia, MDS, or untreated disease who were unwilling to proceed with conventional systemic chemotherapy were eligible. Other eligibility criteria included age of 18 years or older; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; adequate hepatic (ie, bilirubin $\leq$ 1.5 mg/dL; ALT $\leq$ 2.5 $\times$ upper limit of normal [ULN] or $\leq$ five times ULN if hepatic abnormality related to leukemia) and renal functions (ie, creatinine $\leq$ 2.0 mg/dL or creatinine clearance $>$ 60 mL/min); no prior chemotherapy, radiation therapy, or investigational anticancer therapy in the previous 2 weeks; absence of CNS involvement by leukemia; and absence of uncontrolled intercurrent illnesses, including infections, cardiac conditions, or other organ dysfunctions. All patients signed an informed consent form according to institutional guidelines and in compliance with the Declaration of Helsinki.

Study Design and Treatment Plan

This study used a classical 3 + 3, phase I design. The starting dosage of sapacitabine was 75 mg orally twice daily (to total 150 mg daily) for 7 consecutive days every 3 to 4 weeks on the basis of safety data from phase I trials in solid tumors. The timing of the subsequent cycles of treatment varied depending on the disease status and toxicities. The dose was escalated to 100, 125, 175, 225, 275, 325, and 375 mg orally twice daily. The dose level of 100 mg was entered with only one patient and was skipped to 125 mg because of the safety data that emerged from a phase I trial in solid tumors. After the DLT and MTD were defined with the twice daily dosage schedule for 7 days, a second dosing schedule of twice daily oral sapacitabine for 3 consecutive days weekly for 2 weeks, every 3 to 4 weeks, was implemented. Dose levels evaluated on this second dosing schedule were 375, 425, and 475 mg twice daily.

DLT and Dose Escalation Rules

A DLT was defined as the occurrence of any clinically significant and drug-related, grades 3 to 4, nonhematologic toxicity despite maximum supportive care, or prolonged pancytopenia in the presence of a hypocellular bone marrow (ie, cellularity 5% or fewer without evidence of leukemia) that lasted longer than 42 days from the start of therapy. Three patients were entered at each dose level. If no DLT was observed, patients were treated at the next-higher dose level. If one DLT was observed, three more patients were treated at that dose level. MTD was defined as the dose that produced grades 3 to 4 toxicity in at least two of six patients treated. The recommended dose for future

phase II studies would be the dose level immediately before the MTD. The duration of therapy was indefinite as long as there was benefit to the patient.

Response and Toxicity Criteria and Statistical Methods

Response criteria were standard.[17,18] Complete remission (CR) in patients with AML or ALL was defined as normalization of the blood and bone marrow with 5% or fewer blasts in normocellular or hypercellular bone marrow, a granulocyte count of 10^9/L or greater, and a platelet count of 100×10^9/L or greater. A partial response (PR) was defined as the same as CR but with at least a 50% decrease to 6% to 25% marrow blasts. A CR without platelet count recovery (CRp) was defined as the same as CR but without platelets recovery to 100×10^9/L or greater. A marrow CR (CRi) was defined as the same as CR but without granulocytes recovery to 10^9/L and/or platelets recovery to 100×10^9/L or greater. Response in MDS was defined according to the modified International Working Group (IWG) criteria.[18]

Table 1. Baseline Demographic and Clinical Characteristics of the Study Group

Characteristic	Patients (N = 47)	
	No.	%
Diagnosis		
AML	42	89
MDS	4	9
ALL	1	2
ECOG performance status		
0	9	19
1	33	70
2	5	11
Treatment status*		
Frontline	7	17
Salvage 1	7	17
Salvage 2	15	36
Salvage 3	4	9
Salvage 4 or more	10	23
Age, years		
Median	65	
Range	35-90	
Prior intensive chemotherapy*	32	74
Karyotype		
Diploid metaphases	12	26
Chromosome 5 or 7 abnormalities	14	30
Non-complex abnormalities (< 3)	7	15
8± other	5	11
Complex abnormalities (≥ 3)	5	11
>Insufficient metaphases	4	9
Hemoglobin, g/dL		
Median	9.6	
Range	7.7-14.3	
WBC, ×10⁹/L		
Median	3.0	
Range	0.3-119.5	
Platelets, ×10⁹/L		
Median	32	
Range	5-353	
Marrow blasts, %		
Median	40	
Range	1-88	
Lactic dehydrogenase, U/L		
Median	564	
Range	277-3,134	

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphocytic leukemia; ECOG, Eastern Cooperative Oncology Group.
*Acute leukemia only (n = 43).

Toxicity was graded on a scale of 0 to 5 by using the National Cancer Institute Common Terminology Criteria of Adverse Events (NCI-CTCAE) version 3.0.[19] The 4-week mortality (from start of sapacitabine) was calculated as a combined measure of the drug efficacy and safety, regardless of a causal relationship to the study drug. Survival and response durations were analyzed by the Kaplan-Meier method.

Clinical Pharmacology

Patients who consented to participate in pharmacokinetic (PK) and pharmacodynamic studies were instructed to fast (ie, no food or drink except water) after midnight before the morning of day 1 of cycle 1. The dose of sapacitabine was administered about 1 hour before breakfast. Peripheral blood samples were taken predose (time 0) and at 1, 2, 4, 6, 8, and 24 hours after the dose of sapacitabine was given. The 24-hour time point for day 1 was obtained in the morning of day 2 before the patient took the second dose of sapacitabine. All blood samples (10 mL) were collected in green stopper vacutainer tubes coated with heparin and containing 400 μmol/L tetrahydrouridine (THU), the latter of which was added to inhibit deamination of CNDAC by cytidine deaminase (CDA). Immediately after collection, the blood samples were chilled in an ice-water bath, and plasma was separated from peripheral-blood mononuclear cells (PBMCs) by centrifugation at 4°C. Plasma samples were stored at −70°C, and cell pellets were processed additionally for pharmacodynamic analysis.

Plasma Pharmacology

Plasmas samples were spiked with radioactive-labeled sapacitabine (carbon-13 nitrogen-15 [$^{13}C^{15}N_4$]) and CNDAC (carbon-13 nitrogen15 [$^{13}C^{15}N_4$]), as the internal standards and levels of sapacitabine and CNDAC were determined by a validated high-performance liquid chromatography and tandem mass spectrometric detection (LC/MS/MS) assay. The lower limits of quantification (LOQs) for sapacitabine and CNDAC were 0.2 ng/mL and 1 ng/mL, respectively. Actual sampling times were used in all PK analyses. The maximum plasma concentration (C_{max}) and time to C_{max} (T_{max}) were taken directly from the data. Because of the lack of a log-linear decay during the 8-hour sampling period, no estimate could be made for the elimination rate constant, λz, and half-life ($t_{1/2}$). Area under the curve from zero to the final sample with a concentration at LOQ or greater (AUC_{0-t}) was calculated by using the linear trapezoidal method. All PK calculations were done and all individual patient plasma concentration–time graphs were prepared by using SAS for Windows version 9.1.3 (SAS Institute, Cary, NC). Graphs of mean plasma concentration versus time were prepared by using SigmaPlot for Windows version 11.0.

Cellular Pharmacology

Cell pellets collected from blood samples were washed with phosphate-buffered saline (PBS). PBMCs were isolated by Ficoll-Hypaque density-gradient centrifugation, were washed with PBS, and were counted with an electronic particle counter. Approximately 1 to 2 × 10^7 cells were used to extract nucleotides, and the nucleotides were separated by strong anion-exchange high-performance liquid chromatography and were quantitated by using ultraviolet absorbance with reference to standards.[20] The remaining cells, if available, were incubated with 1.0 μCi hydrogen-3–thymidine for 30 minutes to determine DNA synthesis in triplicates of 2 × 10^6 cells.

RESULTS

Patient Characteristics and Treatment Administration

A total of 47 patients were treated. The characteristics are listed in Table 1. The median age was 65 years (range, 35 to 90 years); 17 patients (36%) were women. Forty-two patients had AML, one had ALL, and four had MDS (Table 1). Seven patients with AML had received no prior chemotherapy. The median number of treatment

Table 2. Dose Escalations and Dose-Limiting Toxicities

Dose level, mg	No. of Patients	Dose-Limiting Toxicity
Twice daily × 7 days	35	
75	3	None
100	1	None
125	3	None
175	3	None
225	3	None
275	6	Diarrhea and neutropenic colitis, grade 3*
325†	9	Diarrhea, grade 3*
375	7	Abdominal pain and small-bowel obstruction, grade 3*; neutropenic colitis, death*
Twice daily for 3 d/wk × 2 weeks	12	
375	3	0
425†	6	0
475	3	Diarrhea, grade 3†

*No. of patients = 1.
†Recommended phase II dose.

Table 3. Patients With Drug-Related Toxicity by Dosing Schedule

	No. of Patients by Dosage Regimen and Toxicity Grade			
	Twice Daily × 7 Days (n = 35)		Twice Daily × 3 d/wk × 2 Weeks (n = 12)	
Toxicity	Grades 1-2	Grades 3-4	Grades 1-2	Grades 3-4
Hematologic				
Anemia	0	1	1	0
Leukopenia	1	6	0	7
Neutropenia	0	5	0	4
Thrombocytopenia	1	1	1	7
Nonhematologic				
Abdominal pain	4	1	0	0
Constipation	2	0	0	0
Diarrhea	9	1	1	1
Nausea	13	0	6	0
Neutropenic colitis	0	2*	0	0
Small bowel obstruction	0	1	0	0
Stomatitis	2	0	1	0
Vomiting	5	0	2	0
Oral mucosal petechiae	0	0	1	0
Mucosal hemorrhage	0	0	1	0
Mucosal inflammation	1	0	0	0
Asthenia	2	0	0	0
Fatigue	6	0	4	0
Increase in ALT	1	0	0	0
Increase in alkaline phosphatase	1	0	0	0
Anorexia	2	0	1	0
Decreased in appetite	1	0	0	0
Dysgeusia	0	0	1	0
Dyspnea	1	0	0	0
Hiccups	1	0	0	0
Alopecia	8	0	1	0
Petechiae	1	0	1	0

*One patient died as a result of neutropenic colitis.

cycles was three (range, one to 16 cycles). Five patients completed six or more treatment cycles, including one patient who completed 16 cycles.

DLTs and MTDs

The number of patients treated at each dose level and the observed DLTs are listed in Table 2. Drug-associated gastrointestinal adverse effects were dose limiting at the sapacitabine dose level of 375 mg orally twice daily for 7 days; this level included one drug-related death as a result of neutropenic colitis. The dose schedule of sapacitabine chosen for phase II studies was 325 mg orally twice daily for 7 days; this schedule could be given frequently (eg, every 3 to 4 weeks), in the outpatient setting, with minimal extramedullary (gastrointestinal) or medullary toxicity that may provide better control of the leukemia.

After the completion of investigation of the 7-day schedule, patients received sapacitabine at 375, 425, and 475 mg orally twice daily for 3 days, weekly for 2 weeks (days 1 through 3 and days 8 through 10). Again, gastrointestinal toxicity was dose limiting at the sapacitabine dose of 475 mg orally twice daily. Although only one patient experienced the DLT of grade 3 diarrhea at this dose level, a decision was made not to expand this dose level because of significant thrombocytopenia observed in another patient who had a decrease in platelet count from normal to less than 10×10^9/L during the first treatment cycle. The phase II recommended dose with this schedule was 425 mg orally twice daily on days 1 to 3 weekly for 2 weeks.

Safety and Tolerability

The most common drug-related adverse events (Table 3) were constitutional (fatigue), gastrointestinal (anorexia, abdominal pain, diarrhea, nausea, and vomiting), and hematologic (neutropenia and thrombocytopenia). Myelosuppression-associated complications in the first course included febrile episodes in 14 patients (30%). These consisted of fever of unknown origin in nine patients (19%) and infections in five patients (11%). Two deaths occurred within 4 weeks of start of therapy. The first death was a 75-year-old man with AML who was treated at the dose level of 375 mg twice daily for 7 days every 21 days. On day 12 of treatment cycle 1, he was admitted to the hospital with abdominal pains and distention, nonbloody diarrhea, and neutropenic fever. No peritoneal signs were present by physical exam. Abdominal CT scan showed no bowel obstruction or free air, but there were slightly prominent loops of small bowel with significant bowel wall thickening. The clinical suspicion was neutropenic colitis. The patient was treated with broad-spectrum antibiotics and bowel rest. Despite aggressive treatment, he developed hypotension, pulmonary insufficiency, and acidosis, and he died on day 22. The death was considered definitely related to the study drug. The second death occurred in a 51-year-old man with refractory AML who died on day 27 with persistent AML, pneumonia, and multiorgan failure.

PKs

PK data were available from 10 patients who received doses of 125 mg (n = 2), 325 mg (n = 4), 375 mg (n = 1), 425 mg (n = 2), and 475 mg (n = 1) twice daily (Table 4). The median T_{max} of plasma sapacitabine for all courses was 120 minutes (range, 60 to 360 minutes), and it was similar for CNDAC (median, 120 minutes; range, 60 to 480 minutes). There was no apparent dose-related change in the individual patient plasma concentrations of sapacitabine or CNDAC on either day 1 or day 8. Similarly, there was no apparent relationship between either C_{max} or AUC_{0-t} and dose for either analyte. Although there was an apparent trend toward an increase in C_{max} and AUC_{0-t} for sapacitabine, the relationships were not significant.

Adequate leukemia blasts for nucleotide pool analyses throughout the sampling time course were recovered from five patients (125 mg, n = 2; 325 mg, n = 2; 475 mg, n = 1). In no case was the level of CNDAC triphosphate quantifiable, likely because the plasma C_{max} concentrations of CNDAC in the range 33 to 250 nmol/L would not generate triphosphate concentrations detectable by ultraviolet absorbance[20] There was no consistent inhibition of DNA synthesis in leukemia blasts observed in the ex vivo assays.

Table 4. Summary of Pharmacokinetic Parameters for Sapacitabine and CNDAC

Parameter	Dose (mg)				
	125	325	375	425	475
Sapacitabine*					
Cycle 1, day 1					
C_{max}, ng/mL	3.16 2.00	35.10 2.14 5.79 27.50	14.90	35.30 15.60	2.77
T_{max}, minutes	250 380	135 65 65 120	119	360 120	240
$AUC_{(0-t)}$, min × ng/mL	755.5 406.7	16,463 181.5 903 3,529	1,671	9,160 2,629	536
Cycle 1, day 8					
C_{max}, ng/mL	5.43	8.88			
T_{max}, minutes	240	360			
$AUC_{(0-t)}$, min × ng/mL	774.7	3,437			
CNDAC*					
Cycle 1, day 1					
C_{max}, ng/mL	15.5 8.23	19.8 2.88 9.98 63.7	6.76	67.3 34.6	11.6
T_{max}, minutes	250 65	135 65 120 120	119	480 120	240
$AUC_{(0-t)}$, min × ng/mL	3,738 1,998	3,100 242.9 1,647 12,169	463.4	18,315 5,325	1,493
Cycle 1, day 8					
C_{max}, ng/mL	4.65	16.9			
T_{max}, min	240	120			
$AUC_{(0-t)}$, min × ng/mL	709.1	4,490			

NOTE. N = 10 patients.
Abbreviations: CNDAC, 2'-C-Cyano-2'-deoxy-β-D-arabino-pentofuranosylcytosine; C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; $AUC_{(0-t)}$, area under the curve from zero to the final sample with a concentration.
*Each value represents an individual patient.

Patient	Age (years)	Diagnosis	Salvage Status	CG	Prior Treatment	Response to Prior Treatment	CRD1	Last CRD	Sapacitabine Twice Daily × 7 or Days 1-3 Each Week × 2 Weeks (mg/m²)	Response Type	Duration of Response (months)
14	59	MDS→EMD	S2	IM	HDAC Allo SCT DLI	NR CR CR	0	4	225 × 7	CR	≥ 3.9
32	66	CMML→AML	S3	del 13q*	Decitabine clofarabine (for MDS)	CR NR	1	0	325 × 7	CRp	2.2
41	57	AML	S1	Diploid	IA	PR		0	425 × 3/wk × 2	CR	≥ 1
45	85	AML	S5	abn 5/7†	DA DA FIA FAM	CR CR CR CR	22	84	475 × 3/wk × 3	CR	≥ 1
12	75	MDS-RAEB	S1	Diploid	Azacitidine		Unknown		225 × 7	BM CR	0.5
13	79	MDS-CMML	S1	Diploid	DAC	CR	15		225 × 7	CR	3.3
6	82	AML	S2	Complex	DAC GO	NR NR	0	0	125 × 7	CRp	2.1
9	53	MDS→AML	S3	Diploid	IA/tipinarnib CDDO	CR NR	3	—	175 × 7	BM CR	2
10	56	AML	S1	IM	IA	CR		1	175 × 7	BM CR	≥ 1.9
15	73	MDS-CMML	S1	Other (noncomplex)	DAC	CR		12	275 × 7	BM CR	2
17	90	MDS→AML	F	Other (noncomplex)	—			—	275 × 7	BM CR	2.5
22	69	Treatment related AML	F	Complex	—			—	325 × 7	BM CR	0.5
23	55	AML/(+EMD)	S4	Diploid	IA IA Flud/AraC	CR CR NR	3	—	325 × 7	BM CR	1.5

Table 5. Characteristics of Responders

(continued on following page)

Response

Overall, 13 patients (28%) achieved objective responses: four had CR, two had CRp, and seven had CRi. Several patients had extensive prior therapy. The details of the patients are listed in Table 5. Two patients with AML had experienced relapsed leukemia cutis with numerous skin nodules. Both patients achieved a significant reduction in the number of skin nodules, and one patient had complete resolution of all skin nodules. In addition to our observations in patients with objective responses, we observed prolonged stable disease in one patient. This patient had AML in second relapse after standard induction chemotherapy. The baseline bone marrow had 34% blasts with an absolute granulocyte count of 0.25×10^9/L. This patient received a total of 16 cycles of treatment and had a reduction in bone marrow blast to as low as 6% and normalization of granulocyte count greater than 10^9/L. In addition, 20 patients (43%) had at least 1-log reduction of peripheral blasts (n = 12) and/or at least 50% reduction of marrow blasts (n = 8). Two patients died in the first 4 weeks of therapy. The estimated 4-week mortality for the total study group was only 4%. Survivals of the overall group and of responders are shown in Figure 1.

DISCUSSION

Sapacitabine is an oral prodrug of CNDAC, a rationally designed analog of deoxycytidine. Despite its structure and chemical simi-

larity to cytarabine, it has unique properties in causing single-strand DNA breaks because of the presence of a cyano group within the deoxyribose moiety of the molecule. As myelosuppression was the DLT in solid tumor studies, we evaluated sapacitabine in a phase I study in acute leukemias and MDS. We defined the new extramedullary DLT to be gastrointestinal. Two phase II dose schedules were recommended for future studies: 325 mg orally twice daily for 7 days every 3 to 4 weeks and 425 mg orally twice daily on days 1, 2, 3 weekly for 2 weeks every 3 to 4 weeks. Although the plasma levels of sapacitabine and CNDAC were highly variable and were not dose proportional, it appears that the sapacitabine dose could be titrated to reach MTD by an increment of 100 mg/d in patients with leukemias and MDS. PK data were available for 10 patients entered into five dose levels that ranged between 125 and 475 mg. Given this relatively small cohort and the inherent variability of oral administration, it is not surprising that a significant dose-response relationship was not evident. Additional clinical studies are presently administering sapacitabine in different schedules at doses within this range and will address more appropriately the sapacitabine dose-response relationship.

The drug was well tolerated and showed encouraging antileukemic activity in the setting of poor-prognosis AML and MDS. Among 47 patients, 13 achieved objective responses, and an additional 20 patients had significant reductions of their blasts. Objective responses also were observed in extramedullary disease (ie, leukemic cutis).

	% BM Blasts		PLTs (× 10⁹/L)		% PB		PMN (× 10⁹/L)		
Patient	Pretransplantation	Post-Transplantation	Pretherapy	Post-Therapy	Pretherapy	Post-Therapy	Pretherapy	Post-Therapy	Comments
14	1	1	72	82	0	0	2.5	1.1	CR of EMD; off therapy because of concurrent disease
32	50	3	38	44	8	0	6.6	1.6	
41	21	3	261	> 100	0	0	2.3	> 1.0	Off for SCT
45	40	2	41	120	0	0	0.5	1.5	Off for consolidation therapy
12	8	4	31	51	4	0	0.1	0.17	
13	17	2	324	372	2	0	0.28	1.3	
6	77	2	45	83	66	0	2.4	3.2	
9	18	1	20	14	1	0	0.7	0.6	
10	14	2	30	42	8	0	1.2	0.18	Off for cord SCT
15	9	5	28	4	0	0	3.3	0.03	
17	40	5	27	32	8	0	0.04	0.34	
22	33	2	24	14	5	0	12.2	0.4	
23	10	4	151	52	0	0	3.4	1.0	> 50% reduction in EMD

Abbreviations: CG, cytogenetics; CRD1, duration of first complete response; CRDlast, duration of last complete response; BM, bone marrow; PLTs, platelets; PB, peripheral blood; PMN, granulocytes; MDS, myelodysplastic syndrome; EMD, extramedullary disease (leukemic cutis); S2, second salvage; IM, insufficient metaphases; HDAC, high-dose cytarabine; NR, no response; CR, complete response; AlloSCT, allogeneic stem-cell transplantation; DLI, donor lymphocyte infusions; CMML, chronic myelomonocytic leukemia; AML, acute myeloid leukemia; S1, first salvage; IA, idarubacin and cytarabine; CDDO, 2-cyano-3, 12 dioxoolean-1, 9-dien-28-oic acid; PR, partial response; SCT, stem-cell transplantation; DA, daunorubicin and cytarabine; FIA, fludarabine, idarubicin, cytarabine; FAM, fludarabine, cytarabine, mitoxantrone; RAEB, refractory anemia with excess blasts; DAC, decitabine; CRp, complete response without platelet recovery; GO, gemtuzumab ozogamicin; S3, third salvage; F, front-line; S4, fourth salvage; Flud, fludarabine; AraC, cytarabine.
*del13q represents deletion in the long arm of chromosome 13.
†abn 5/7 represents chromosome 5 or 7 abnormalities.

The prognosis of patients with AML remains poor. Overall, only 25% to 30% of patients with newly diagnosed disease are cured. The prognosis is significantly worse in elderly patients with AML and in patients who have AML with poor karyotypes, for whom the cure rates are less than 10%. In elderly patients with AML, standard intensive chemotherapy is associated with a high mortality rate (ie, 30% to 50% in the first 6 to 8 weeks).[3] Such patients may benefit from novel agents, like sapacitabine, that provide antileukemic efficacy and ease of administration (oral outpatient therapy) without the concurrent high mortality.

Although survival of patients with MDS has improved with the introduction of hypomethylating agents, the prognosis remains poor. The median survival of patients with higher-risk MDS treated with azacitidine is only 20 to 25 months. Once patients with MDS experience failure on therapy with hypomethylating agents, the prognosis is poor; the median survival after failure of hypomethylating-agent therapy is only 4 to 6 months.[21] Therefore, effective anti-MDS agents are needed for this orphan indication. Randomized studies of sapacitabine to evaluate different dose schedules are ongoing in elderly patients with newly diagnosed or first-relapsed AML and in patients with MDS who have failed hypomethylating agents.

In conclusion, sapacitabine has demonstrated a reasonable safety profile in this phase I study and has encouraging antileukemic activity. Current studies are evaluating its role as a single agent in elderly patients with AML and in MDS. The development of combinations of sapacitabine with other antileukemic agents is warranted.
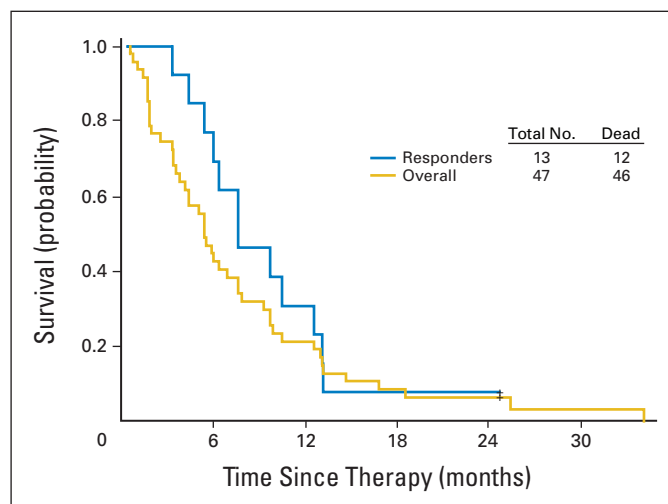

Fig 1. Survival overall and in responders.

	Total No.	Dead
Responders	13	12
Overall	47	46

AUTHOR CONTRIBUTIONS

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