

Phase I Study Of Sapacitabine, An Oral Nucleoside Analogue, In Patients With Advanced Leukemias Or Myelodysplastic Syndromes

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INTRODUCTION

Sapacitabine is a novel nucleoside analogue

- Orally available
- Converted by amidases to CNDAC
- CNDAC is activated by deoxycytidine kinase to become CNDAC-triphosphate
- CNDAC is less susceptible to inactivation by cytidine deaminase than ara-C

CNDAC triphosphate

- Inhibits DNA synthesis by being an efficient substrate for DNA polymerase α
- Causes DNA single strand break by β -elimination (unique mechanism of action)
- Induces G2-phase arrest as compared to S-phase arrest by ara-C and gemcitabine

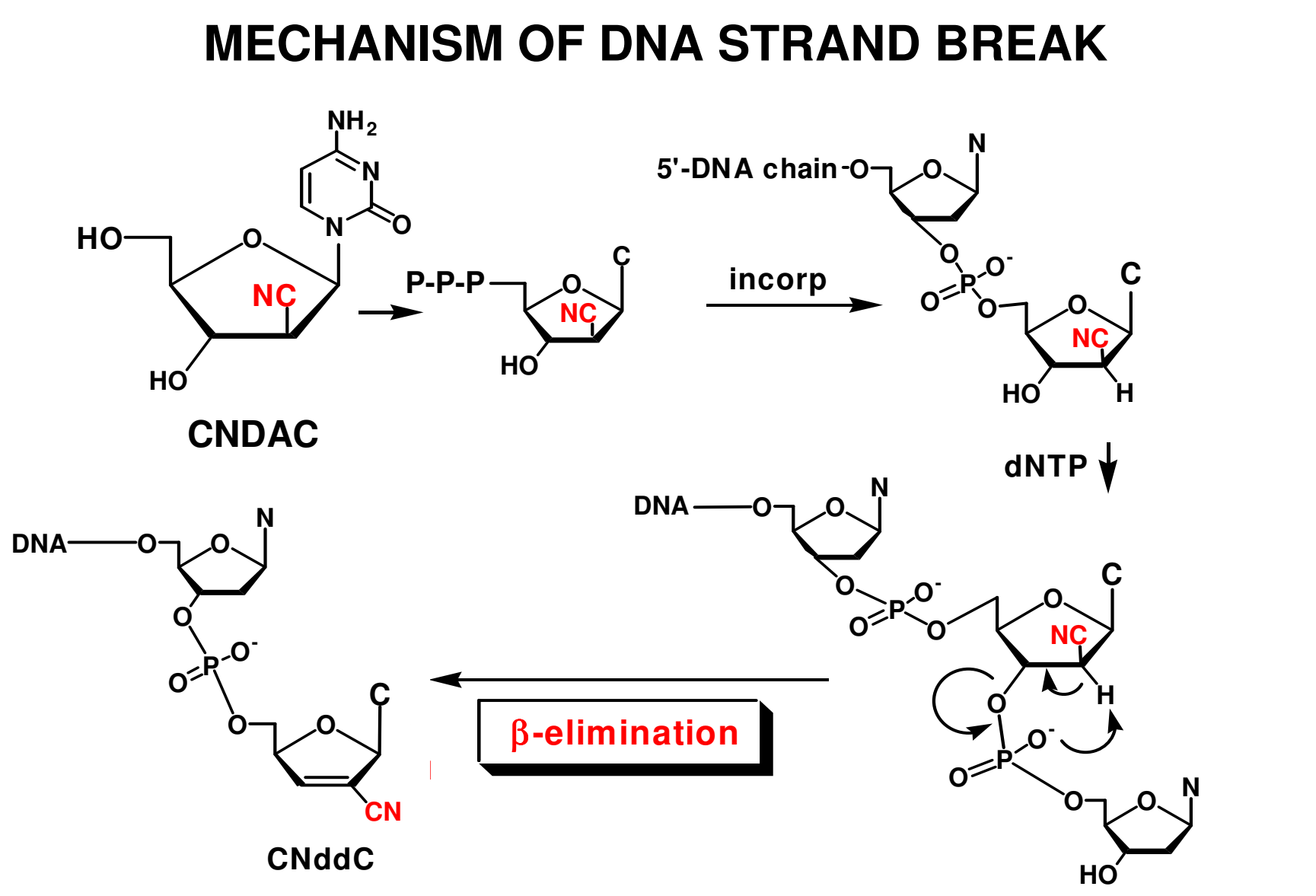
Active against both hematologic malignancies and solid tumors in *in vitro* and *in vivo* in animal models

- More active than ara-C in a P388 leukemia model
- More active than gemcitabine or 5-FU in a colon cancer liver-metastasis xenograft model

References

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The poster contains updated interim data (unaudited)



- ### STUDY RATIONALE
- Nucleoside analogues, e.g., ara-C, fludarabine, decitabine and azacitidine, are active against leukemias and MDS
 - Despite the availability of these agents, patient outcome remains poor because responses are generally not durable and treatments induce significant toxicities
 - New effective drugs are required to improve the outcome of these diseases
- ### METHODS
- An open label dose-escalation study of twice daily dosing (b.i.d.)
 - b.i.d. x 7 consecutive days every 21 days
 - b.i.d. x 3 consecutive days/week x 2 weeks every 21 days
 - The primary objective is to determine the maximum tolerated dose (MTD); secondary objectives are to characterize PK/PD effects
 - Major eligibility criteria
 - Relapsed/refractory leukemias or MDS, or untreated disease if not willing to proceed with conventional systemic chemotherapy
 - ECOG performance status 0-2
 - Adequate organ functions
 - Signed informed consent form
 - At least 3 patients to be entered at each dose level
 - At least 6 patients to be treated at the recommended Phase II dose (RD) to confirm tolerability

- ### DLT and MTD
- DLT is defined as the occurrence of any of the following events during the first treatment cycle when judged to be clinically significant and related to sapacitabine treatment
 - Grade 3/4 nausea, vomiting, or diarrhea despite maximum supportive care
 - Other Grade 3/4 non-hematological toxicity with the exception of alopecia
 - Pancytopenia with a hypocellular bone marrow ($\leq 5\%$ cellularity) and no evidence of leukemia, lasting longer than 42 days
 - MTD is the highest dose level at which ≤ 2 of 6 patients experienced a DLT during the first treatment cycle
 - Recommended Phase II dose (RD) is the dose level immediately below the MTD

PATIENT CHARACTERISTICS

	Number of Patients (n=47)
Age in years, median (range)	66 (36-91)
<60	18
≥ 60 to 69	10
≥ 70 to 79	12
≥ 80	7
Gender	30
Male	17
Female	17

DOSE-LIMITING TOXICITY

Dosing Schedule	DLTS
b.i.d. x 7d q 21 days	
75, 100, 125, 175 and 225 mg (n=13)	0
275 mg (n=6)	Diarrhea/neutropenic colitis- grade 3 (n=1)
325 mg (n=9)	Diarrhea-grade 3 (n=1)
375 mg (n=7)	Abd pain and small bowel obstruction-grade 3 (n=1) Neutropenic colitis - death (n=1)
b.i.d. x 3 d/wk x 2wks q 21 days	
375 mg (n=3)	0
425 mg (n=6)	0
475 mg (n=3)	Diarrhea-grade 3 (n=1)

COMMON ADVERSE EVENTS (all cycles, all dose levels, regardless of causality, n=47)

AE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Abdominal pain	5	7	3	0	0
Anorexia	7	7	2	0	0
Asthenia	3	6	2	0	0
Cough	12	1	0	0	0
Dyspnea	3	6	3	0	0
Diarrhea	14	6	3	0	0
Fatigue	8	11	2	1	0
Febrile neutropenia	0	0	20	0	1
Hypokalemia	5	2	8	0	0
Hypomagnesium	11	1	0	0	0
Leukopenia	1	3	11	0	0
Nausea	10	12	1	0	0
Thrombocytopenia	0	2	1	8	0
Vomiting	10	4	1	0	0

DISEASE CHARACTERISTICS

Disease	Number of Patients (n=47)
AML	25
De novo	1
Treatment-related	16
Preceded by MDS	4
MDS	4
RAEB	1
ALL	1
Prior Chemotherapies	6
0	26
1- 2	15
≥ 3	34
Prior Chemotherapies	17
Ara-C	7
Decitabine or azacitidine	17
Allo SCT or BMT	7

SCT = stem cell transplant; BMT = bone marrow transplant

ACCRUAL PER DOSE LEVEL

Dosing Schedule	Number of Patients Treated (n=47)
b.i.d. x 7 days q21 days (n=35)	75 mg (n=3)
	100 mg (n=1)
	125 mg (n=3)
	175 mg (n=3)
	225 mg (n=3)
	275 mg (n=6)
	325 mg (n=9)*
	375 mg (n=7)
b.i.d. x 3 days/wk x 2 wks q21 days (n=12)	375 mg (n=3)
	425 mg (n=6)*
	475 mg (n=3)

*Recommended Phase II dose

BEST RESPONSE

Dosing (mg b.i.d.)	Patient	Age	Disease	Prior Therapies	Best Response	Treatment Cycles
125 x 7d (n=3)	006	82	De novo AML	Ara-C/Ida, Mylotarg	CRp	7
175 x 7d (n=3)	009 010	53 56	AML pre by MDS De novo AML	Ara-C/Ida, CDDO Ara-C/Ida/Zarnestra	Marrow blasts 18% \downarrow to 1% Marrow blasts 14% \downarrow to 2%	5 2*
225 x 7d (n=3)	012 013 014	75 79 59	MDS-RAEB MDS-RAEB AML pre by MDS/skin	Azacitidine Decitabine Ara-C, Allo BMT	Marrow blasts 8% \downarrow to 4% CR CR	3 11 3
275 x 7d (n=6)	015 017 020	73 91 62	MDS-RAEB AML pre by MDS De novo AML	Decitabine None Ara-C/daunorubicin, Gleevec	Marrow blasts 9% \downarrow to 5% Marrow blasts 40% \downarrow to 5% Marrow blasts 82% \downarrow to 14%	3 4 4
325 x 7d (n=9)	022 023 032	70 55 66	AML treatment-rel De novo AML/skin AML pre by MDS	None Ara-C/daunorubicin, Ara-C/fludarabine Decitabine, clofarabine	Marrow blasts 33% \downarrow to 2% Marrow blasts 10% \downarrow to 4% 50% \downarrow in skin nodules (PR) CRp	7 2 4
375 x 7d (n=7)	024 026 030	72 65 65	AML pre by MDS AML pre by MDS AML pre by MDS	Azacitidine Azacitidine, topotecan Ara-C/clofarabine, Allo SCT	Marrow blasts 60% \downarrow to 24% Marrow blasts 25% \downarrow to 12% Marrow blasts 12% \downarrow to 6%	2 6 2
375 x 3d (n=3)	037	45	De novo AML	Ara-C/Ida	Marrow blasts 40% \downarrow to 22%	2
425 x 3d (n=6)	041 047 048	58 83 68	De novo AML De novo AML AML pre by MDS	Ara-C/Ida None Ara-C/Ida, Ara-C/clofarabine	CR Marrow blast 57% \downarrow to 15% Marrow blast 60% \downarrow to 24%	4* 4 4
475 x 3d (n=3)	043 045	81 86	De novo AML De novo AML	Dasatinib Ara-C/Ida, Mylotarg, fludarabine	Marrow blast 34% \downarrow to 19% CR	>4 2**

CR = complete remission; CRp = complete remission without platelet recovery
 *went on to receive bone marrow transplant; ** went on to receive consolidation therapy

SUMMARY

- Oral nucleoside analogue with unique mechanism of action and novel biological response, i.e., G2-phase arrest
- DLT is gastrointestinal toxicity in patients with advanced leukemias or MDS
- The RD is 325 mg b.i.d. x 7 days every 21 days or 425 mg b.i.d. x 3 days/week x 2 weeks every 21 days
- Anti-leukemic activity observed in relapsed/refractory AML and MDS
- Further clinical studies in these diseases are warranted

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