Phase I/II study of sapacitabine and decitabine administered sequentially in elderly patients with newly diagnosed acute myeloid leukemia.

Sub-category:
Leukemia

Category:
Leukemia, Myelodysplasia, and Transplantation

Meeting:
2011 ASCO Annual Meeting

Abstract No:
6587

Citation:
J Clin Oncol 29: 2011 (suppl; abstr 6587)

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Abstract Disclosures

Abstract:

Background: Sapacitabine is a novel nucleoside analogue with a unique ability to cause irreparable single-strand DNA breaks and induce G2 cell cycle arrest. It is orally administered and has demonstrated promising activity in patients with acute myeloid leukemia (AML). In AML cell lines, the active metabolite of sapacitabine, CNDAC, is synergistic with hypomethylating agents with the synergy being more apparent if cells are treated with hypomethylating agents first. We are conducting a phase 1/ 2 study to evaluate the safety and efficacy of administering sapacitabine in alternating cycles with decitabine in elderly patients with newly diagnosed AML. **Methods:** Decitabine 20 mg/m^2 is infused intravenously daily x 5 days of a 4-weeks cycle (odd cycles) alternating with sapacitabine 300 mg po *b.i.d.* x 3 days/week x 2 weeks of a 4-weeks cycle (even cycles). These doses are considered tolerable if dose limiting toxicity (DLT) occurs in ≤ 2 of 6 patients in the phase 1. The planned sample size for phase 2 is 24 patients including those who receiving the same doses of both drugs in the phase 1. The primary efficacy endpoint is response rate (CR, CRp, PR, or major HI). The regimen will be considered active if response rate is ≥ 30%. Eligible patients must be ≥70 years with untreated AML, unsuitable for or unwilling to receive standard induction chemotherapy; patients who received hypomethylating agents for prior MDS or MPD are excluded. **Results:** As of January 2011, 21 patients were treated with the above regimen and 16 had ≥ 60 days of follow-up. Median age is 76 years (range, 72-88). No DLT were observed. Three patients achieved CR, 2 PR and 1 major HI in platelets. Time to response is 2-4 cycles. Eight patients have received ≥ 4 cycles of treatment. Two patients died within 60-days and the deaths were unrelated to study drugs by investigator assessment. Common adverse events (regardless of causality) included weakness, anorexia, nausea, diarrhea, dehydration, dyspnea, edema, pneumonia, febrile neutropenia, neutropenia, thrombocytopenia, anemia, and hypocalcemia, mostly moderate in intensity. **Conclusions:** The sequential combination of decitabine and sapacitabine is safe and active in elderly AML.

PHASE 1/2 STUDY OF SAPACITABINE AND DECITABINE ADMINISTERED SEQUENTIALLY IN ELDERLY PATIENTS WITH NEWLY DIAGNOSED AML

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SAPACITABINE

A novel, orally available, 2'-deoxycytidine nucleoside analogue. Converted to CNDAC in vivo. CNDAC activated by deoxycytidine kinase to CNDAC-triphosphate

- An efficient substrate for DNA polymerase α for incorporation into DNA
- Introduces single strand DNA breaks via β-elimination reaction converted to double strand DNA breaks after several replication cycles resulting in cell death
- DNA damage repaired by the homologous recombination pathway

Active in combination with other anti-cancer agents in preclinical studies

- Hypomethylating agents: decitabine, azacitidine *(Green S et al, AACR, 2009)*
- HDAC inhibitors: butyrate, valproate, vorinostat *(Green S et al, Br J Cancer, 2010)*
- c-Abl inhibitor: imatinib *(Xiajun Liu et al, minisymposium, AACR, 2011)*
- PARP inhibitor: olaparib, veliparib *(Xiajun Liu et al, minisymposium, AACR, 2011; Frame et al., 14th Congress of the EHA, 2009)*

STUDY RATIONALE

AML most common in older patients but treatment outcomes disappointing

Older patients less likely than younger patients to achieve a CR to standard induction chemotherapy. For those who achieve a CR, there is a high rate of leukemia relapse due to a lack of effective and tolerable post-remission therapy.

Median survival by standard induction therapy is only 4.9 months for the majority of patients who are 70 years or older *(Kantarjian H et al, Blood, 2010)*.

- 4-week death rate: **26%**
- 8-week death rate: **36%**

New effective drugs are required to improve the outcome of this disease

Decitabine and sapacitabine have good tolerability and promising anti-leukemic activity in AML *(Cashen F et al, JCO, 2009, Kantarjian H et al, ASH, 2009)*.

Sequential administration of decitabine and sapacitabine in alternating cycles will maximize the efficacy of both drugs and minimize overlapping myelosuppression.

STUDY DESIGN

Open-label, non-randomized, multi-center, Phase 1/2 study

Decitabine: 20 mg/m² infused over 1 hour per day x 5 consecutive days on cycle 1, 3, 5, and subsequent odd cycles

Sapacitabine: 300 mg b.i.d on days 1-3 and 8-10 on cycle 2, 4, 6 and subsequent even cycles

Major eligibility criteria

- 70 years or older
- Newly diagnosed AML with low-intensity therapy as the treatment of choice by Investigator or patient
- ECOG performance status 0-2
- Adequate organ function
- Signed informed consent form

Primary objective: evaluate safety and efficacy of administering sapacitabine in alternating cycles with decitabine

- Safety threshold: DLT ≤ 33%
- Efficacy threshold: ≥ 30% response rate (CR, CRp, PR or major HI)

Sample size: 24 patients treated with recommended Phase 2 dose (RD)

STUDY DESIGN: DLT & MTD

DLT occurs in cycles 1 and 2 when judged to be clinically significant and related to decitabine and/or sapacitabine treatment:

- Grade 3/4 nausea, vomiting, or diarrhea despite maximum supportive care
- Other Grade 3/4 non-hematological toxicity
- Pancytopenia with a hypocellular bone marrow (≤ 5% cellularity) and no evidence of leukemia, lasting longer than 42 days

Recommended Phase 2 dose (RD) or MTD is the highest dose level at which ≤ 2 of 6 patients experienced a DLT during the first 2 treatment cycles

FIGURE 1: MECHANISM OF DNA STRAND BREAK

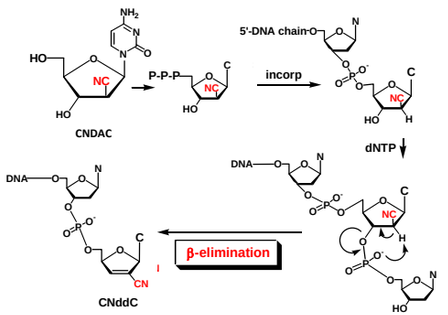

TABLE 1: DEMOGRAPHICS *(patients treated n=23)*

Age (years):	
70 - 74	7 (30%)
75 – 79	9 (39%)
80 or older	7 (30%)
Gender	
Female	9 (39%)
Male	14 (61%)
ECOG	
0 - 1	15 (65%)
2	8 (35%)

TABLE 2: DISEASE CHARACTERISTICS *(patients treated n=23)*

AML Type	
de novo	20 (87%)
preceded by MDS or MPD	3 (13%)
Baseline bone marrow blasts (%)	
20 - < 30%	5 (22%)
30 - < 50%	6 (26%)
≥ 50%	12 (52%)
Peripheral WBC	
< 10 x 10^9/L	13 (57%)
≥10 x 10^9/L	10 (43%)
Peripheral absolute blood blast counts	13 (57%)
< 1 x 10^9/L	8 (35%)
1- 10 x 10^9/L	2 (8%)
>10 x 10^9/L	
Cytogenetics risk by SWOG	
Intermediate/unknown	12 (52%)
Unfavorable	8 (35%)
Not available	3 (13%)

TABLE 3: COMMON ADVERSE EVENTS *(n=22, all cycles, maximum grade, regardless of causality)*

Preferred Term	*All Grades*	*Grade 2*	*Grades 3-4*
Anemia	8	-	8
Febrile neutropenia	5	-	5
Neutropenia	13	-	13
Thrombocytopenia	14	1	13
Atrial fibrillation	3	-	3
Anorexia	4	3	1
Constipation	5	4	1
Dehydration	3	3	-
Diarrhea	3	3	-
Dyspnea	4	4	-
Edema limb	5	5	-
Fatigue	4	3	1
Hypocalcemia	6	3	3
Hypokalemia	3	2	1
Insomnia	3	3	-
Nausea	3	3	-
Pneumonia	6	-	6
Weakness	5	4	1

TABLE 4: SAFETY *(patients treated n=23)*

Remaining on study	12
Follow-up (days): mean (range)	131 (10 – 267)
≥ 60-day follow-up	21
Treatment discontinuation (death and progression)	9
First cycle (death, PD)	2
Second cycle (death, PD)	3
Number of cycles: mean (range)	4 (1 - >9)
≥ 4 cycles	14/21 (61%)
Death, regardless of causality	
30-day	1/21 (5%)
60-day	2/21 (10%)
Dose-limiting toxicity	0
Patients with dose reductions	
Decitabine	0
Sapacitabine *(dose reduction taken for cycle 4 after bone marrow blasts ↓ to < 5%)*	2

TABLE 5: EFFICACY

Age (yrs.)	*WBC (abs. blast)*	*Marrow blasts (%)*	*Cytogenetics (SWOG)*	*Best Response*	*Time to Response (cycles)*	*Total cycles*
72	15.2 (4.86)	61	Unfavorable	marrow blasts ↓ to 17%	3	5
76	3.7 (0.15)	34	Intermediate	marrow blasts ↓ to 16%	3	>8
75	3.2 (0)	45	Intermediate	marrow blasts ↓ to 9%	2	5
78	1 (0)	86	Intermediate	CR	3	>9
74	39 (3.12)	37	Unknown	PR (marrow blasts ↓ to 9%)	3	>7
84	2.3 (0)	21	Intermediate	PR (marrow blasts ↓ to 10%)	2	>7
81	11.5 (4.02)	73	Intermediate	marrow blasts ↓ to 20%	2	5
77	44.2 (20.33)	37	Intermediate	PR (marrow blasts ↓ to 14%)	2	5
74	33.4 (5.34)	63	Unknown	CR	2	5
75	2.8 (0)	23	Intermediate	marrow blasts ↓ to 3%	4	>5
79	2.1 (0.08)	22	Unfavorable	CR	2	>6
72	8.9 (2.49)	71	Intermediate	marrow blasts ↓ to 9%	3	>5
79	1.6 (0.29)	30	Unfavorable	Major HI in ANC and Plt, marrow blasts ↓ to 1%	3	>4
79	14.5 (2.03)	26	Not available	Major HI in Plt, marrow blasts ↓ to 0%	4	>4

SUMMARY

Sequential decitabine and sapacitabine administration is well tolerated

Sufficient anti-leukemic activity for further evaluation in the Phase 3 setting

- **30-day all-cause mortality: 5%**
- **60-day all-cause mortality: 10%**
- **Dose-reduction: 10% (sapacitabine only)**
- **Received ≥ 4 cycles: 61%**
- **Response rate (CR, CRp, PR and major HI): 35%**
- **An additional 6 patients (26%) stayed on study > 4 cycles with ↓ in bone marrow blast counts despite not meeting criteria of response**

Abstract # 6587, ASCO Annual Meeting June 3-7, 2011. Poster contains interim data (unaudited) of an ongoing study as of May 2011. Supported by Cyclacel Ltd.