CLORETAZINE® (VNP40101M) HAS SIGNIFICANT ACTIVITY AS INDUCTION THERAPY FOR ELDERLY PATIENTS (pts) WITH ACUTE MYELOID LEUKEMIA (AML) OR ADVANCED MYELODYSPLASTIC SYNDROME (MDS)

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ABSTRACT

Background: The incidence of AML increases with age with a median age of 68 years at diagnosis. Elderly pts with AML are more likely to have adverse prognostic factors related to the biology of the disease (adverse cytogenetics, history of MDS or prior exposure to cytotoxic agents, increased expression of multi-drug resistance) and medical comorbidities. Little progress has been made in improving outcomes in older pts. Despite variations on the "7+3" regimen, most elderly pts do not receive cytotoxic chemotherapy; pts who are treated with current regimens have lower response rates and overall survival, as well as poor tolerance of side effects, compared to younger pts. New agents are required to increase complete remission (CR) rate and duration with improved safety in this population. Cloretazine® is a novel alkylating agent that has shown significant anti-leukemia activity in vitro and in vivo models.

Aims: A multi-center Phase II study was conducted to investigate activity and safety of Cloretazine® in pts ≥60 years old with newly diagnosed AML or high risk MDS.

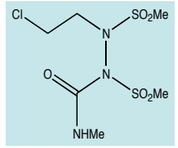
Methods: Cloretazine® was administered at 600 mg/m^2 as a single 30-60 min. IV infusion on day 1. Hydroxyurea 30mg/kg bidx6 was administered starting on day 1. Second induction was allowed for patients who showed improvement. Patients who achieved CR/CRp could receive a consolidation course of Cloretazine® at 400 mg/m^2.

Results: 105 pts were treated (104 evaluable), median age 72 (range 60-84), of whom 44 (42%) had de novo AML, 45 (43%) had secondary AML and 15 (15%) had high risk MDS. Twenty-nine pts achieved a CR and 4 pts a CRp for an overall response rate of 32%. Response in 44 de novo AML, 45 secondary AML and 15 high risk MDS patients was 50%, 11% and 40%, respectively. Response by cytogenetics was 39% in 56 intermediate pts and 24% in 46 unfavorable pts. The CR rates achieved with Cloretazine® are consistent despite increasing age and declining performance status. Severe drug-related non-hematologic toxicity was rare. Eighteen (17%) pts died within 30 days of receiving Cloretazine®. The 1-year overall survival for all treated pts (N=104) was 12%, and 28% for pts with CR (N=33). Patients with de novo AML who achieved CR had a median survival of 6 months and a 1-year survival of 30% (N=22).

Conclusion: Cloretazine® is well tolerated and has significant activity in an elderly patient population with AML or MDS. The encouraging activity in patients with de novo AML warrants further evaluation.

INTRODUCTION

Drug Properties



Cloretazine® (VNP40101M)

- Sulfonylhydrazine alkylating agent
- Upon activation, metabolites alkylate O^6 position of guanine, inhibit AGT, and increase DNA cross-linking
- Active in L1210 cell lines (BCNU, cyclophosphamide, and melphalan resistant)
- Crosses blood-brain barrier

Challenges in the Elderly

- Leukemia-related risk factors
  - Unfavorable cytogenetics
  - Increased MDR expression
  - Increased secondary AML
- Patient-related risk factors
  - Age ≥60 years
  - Decreased functional status
  - Medical comorbidities (cardiac, hepatic, pulmonary)
  - Decreased hematopoietic reserves

RATIONALE

- AML: Disease of an Aging Population
  - Incidence increases from 1 per 100,000 at age 40 to 15 per 100,000 at age 75 and older
  - Median age at diagnosis is 68 years
  - Rapidly aging world population
  - Treatment has changed little over the past 20 years
  - Outcomes after standard treatment are poor
  - Lower tolerance of chemotherapy
  - Higher treatment-related mortality
  - Lower rates of response, higher relapse rates, reduced survival
- Only 10-20% patients are healthy enough to receive standard "7+3" anthracycline/cytarabine induction regimen
- Therapeutic options for the elderly with AML are limited
  - 70% of patients receive best supportive care/palliation[1]
  - NCCN/ESMO guidelines recommend investigational therapy
- ~30% of patients in cooperative group trials are >60 years

[1] *Lang et al., Drugs Aging 2005; 22(11)*

OBJECTIVES

- Further evaluate safety and efficacy of Cloretazine® in Phase II study
- To determine the complete response rate (CR and CRp) of Cloretazine® in elderly patients with AML or high risk myelodysplasia

STUDY DESIGN

Treatment

- Single agent open label trial
- Cloretazine® 600 mg/m^2 IV as a single infusion over 30-60 min, day 1
- Hydroxyurea 30 mg/kg bid x 6 starting day 1
- Induction 2 at same dose for patients with improved bone marrow
- Consolidation at physician discretion using Cloretazine® at 400mg/m^2 IV as a single dose

Eligibility

- Patients ≥ 60 with confirmed AML (FAB type M0, M1, M2, M4-7, excluding M3), or high-risk MDS (IPSS score ≥ 1.5)
- No prior cytotoxic treatment for leukemia
- ECOG performance status of 0-2
- Serum creatinine ≤ 2.0 mg/dl, total bilirubin ≤ 2.0 mg/dl, ALT or AST ≤ 5x the upper limit of normal
- No active uncontrolled infection
- No active heart disease including MI within previous 3 months, symptomatic coronary artery disease, arrhythmias not controlled by medication, or uncontrolled congestive heart failure
- No concurrent disulfiram (Antabuse) or any other standard or investigational treatment for leukemia

RESULTS

Table 1: Demographics of Study Population

No. of patients	109
No. pts ≥ 60 yrs treated (evaluable)	105 (104)
Age (median, range)	72 (60-84)
Diagnosis	
de novo AML	44 (42%)
Secondary AML	45 (43%)
High-risk MDS	15 (15%)
Cytogenetics	
Favorable	0
Intermediate (normal, +8, -Y)	56 (55%)
Unfavorable	46 (45%)
ECOG Performance Status	
0	24 (23%)
1	49 (47%)
2	31 (30%)

Table 2: Clinical Response

Diagnosis (N)	CR/CRp	Overall Response (% within group)
de novo AML (44)	20/2	22 (50%)
Secondary AML (45)	5/0	5 (11%)
MDS (15)	4/2	6 (40%)
Total (104)	29/4	33 (32%)[2]

[2] *4 patients required 2 induction courses to achieve CR*

Clinical Response by Cytogenetic Risk

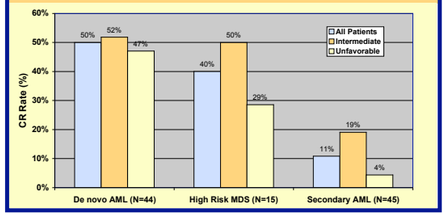


Table 3: Clinical Response by Age and PS

	Age 60-69		Age 70+	
	All pts (%)	Responders (%)	All pts (%)	Responders (%)
PS 0	9 (25%)	2 (22%)	15 (22%)	5 (33%)
PS 1	20 (56%)	10 (50%)	29 (43%)	5 (17%)
PS 2	7 (19%)	2 (29%)	24 (35%)	9 (38%)
Total	36 (35%)	14 (39%)	68 (65%)	19 (28%)

Table 4: Adverse Events

Event	Worst Grade per pt (N=104 pts)					
	1-2	3	4	5	Total N	%
Infusion-related symptoms	60	4	1	0	65	63%
Gastrointestinal disorders	53	4	0	0	57	55%
Non-Infectious pulmonary disorders	20	7	2	0	29	28%
Infection including febrile neutropenia	7	14	6	1	27	26%
Constitutional disorders	19	4	1	0	24	23%
Skin/Rash	14	3	0	0	17	16%
Cardiac disorders	7	0	1	1	8	8%
Neurologic dysfunction	6	2	0	0	8	8%
Metabolic changes	5	2	0	0	7	7%
Eye disorders	5	0	0	0	5	5%
Hepatic disorders	0	2	2	0	4	4%
Renal dysfunction	1	2	1	0	4	4%
Vascular disorders	3	0	0	0	3	3%
Musculoskeletal disorders	2	0	0	0	2	2%
Total N Events	202	44	14	2	260	
%	78%	17%	5%	1%	100%	

Table 5: Myelosuppression

Grade 4 Neutropenia	92%
Grade 4 Thrombocytopenia	82%
Median time to ANC recovery (>1,000)	31 days
Median time to Platelet recovery (>20,000)	22 days
Median time to Platelet recovery (>100,000)	30 days

Table 6: Summary of Early Deaths

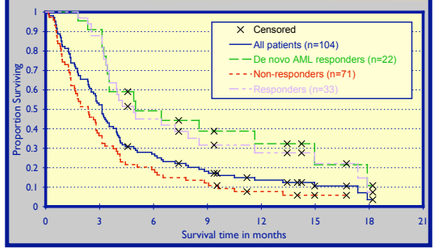
Primary Cause	N
Progressive Leukemia	5
Infection	8
Cardiovascular	1
Multi-organ Failure	2
Respiratory Failure	2
Total	18 (17%)

Table 7: Survival

Responders[3]	
Median survival	5 months
Overall survival at 1 year	28%
Disease-free survival at 1 year	16%
Non-responders	
Median survival	2.5 months
Overall survival at 1 year	6%

[3] *Of 33 pts who achieved CR, 19 (58%) received consolidation*

Overall Survival



CONCLUSIONS

- Cloretazine® induces remissions (CR/CRp) in elderly previously untreated patients with AML and high-risk MDS
- No significant difference in CR/CRp with Cloretazine® despite increasing age and PS
- Cloretazine® achieves CR/CRp in de novo or MDS pts with either intermediate or unfavorable cytogenetics
- Cloretazine® is well-tolerated with expected myelosuppression and minimal non-hematologic toxicity

FUTURE DIRECTIONS

- A confirmatory Phase II trial in elderly patients (≥60y) with untreated de novo poor-risk AML is underway
- Explore use of Cloretazine® in combination with other agents for induction in other patient populations with AML

ACKNOWLEDGMENTS

North American Sites

- **Cleveland Clinic**; Cleveland, OH/*Advani*
- **St. Francis**; Hartford, CT/*Bilgrami*
- **Cornell**; New York, NY/*Feldman*
- **Johns Hopkins**; Baltimore, MD/*Karp*
- **IOHC**; Indianapolis, IN/*Cooper & Khan*
- **MDACC**; Houston, TX/*O'Brien*
- **Duke**; Durham, NC/*Rizzieri*

European Sites

- **Medway Maritime**; UK/*Aldouri*
- **Academisch Ziekenhuis**; Netherlands/*Daenen*
- **Clinique Universitaire Saint Luc**; Belgium/*Ferrant*
- **King's College**; UK/*Mufti*
- **UZ Gasthuisberg**; Netherlands/*Verhoef*
- **Institut Paoli-Calmettes**; France/*Vey*
- **Leyenburg Ziekenhuis**; Belgium/*Wijermans*

EHA 2006