Cloretazine® Is An Effective Induction Therapy in Elderly Patients with Poor-Risk *de novo* AML

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ABSTRACT

Background: The incidence of AML increases with age with a median of 68 years in the US. The treatment of elderly pts (>60 years) with AML poses challenges related to pt characteristics (age, performance status (PS), medical comorbidities) and adverse biological features. The majority of elderly pts are not considered for standard induction therapies that incorporate araC + anthracycline, and complete remission rates (CR+CRp), leukemia-free (LFS) and overall survival (OS) are significantly lower than in younger pts. As a result, NCCN guidelines recommend investigational therapy for this population. Cloretazine® is a novel DNA alkylating agent that selectively targets the O^6 position in guanine and has been developed in AML, based on phase I data demonstrating activity in refractory hematologic malignancies with acceptable toxicity. **Methods:** A multi-center trial in elderly pts with untreated poor-risk AML and high risk MDS was performed. Pts received Cloretazine® (600 mg/m^2) as a single 30-60 minute infusion. Retreatment for induction was permitted for pts who showed improvement. A consolidation course of Cloretazine® at 400 mg/m^2 was an option for pts who achieved a CR. **Results:** 104 pts over 60 were treated, of whom 44 pts (median age 72, range 60-84) had *de novo* AML, 45 had secondary AML preceded by an antecedent hematologic disorder, and 15 had high-risk MDS. Considering only the *de novo* AML pts, pt characteristics are the following: M/F=24/20; favorable/intermediate/poor/NA cytogenetics =0/27(61%)/17(39%)/2; and PS 0/1/2=8(18%)/21(48%)/15(34%). The CR rate in *de novo* AML was 50% (N=22). CR was 52% for intermediate cytogenetics and 47% for poor risk cytogenetics. CR remained consistent despite increasing PS (PS0=50%, PS1=48%, PS2=53%). For responders, the median time for ANC>1000 cells/dl were 31 days (range, 27-44) and for plt>20,000/dl were 22 days (range, 14-29). There was no significant non-hematologic toxicity; the early death rate was 18%. Of the 22 pts who achieved CR, 4 remain alive and disease-free at a median of 407 days (range, 315-671). At one year, the leukemia-free and overall survival is 20% and 30%, respectively. **Conclusion:** Cloretazine® is very well tolerated and has demonstrated impressive response results as a single agent in an elderly pt population with poor risk AML.

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**
- **Elderly Patients with AML/MDS Induction Therapeutic Options**
  - 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 "3+7" anthracycline/cytarabine induction regimen
  - Therapeutic options for the elderly with AML are limited
    - 70% of patients receive best supportive care/palliation*
    - Investigational or experimental therapy---NCCN/ESMO guidelines
  - Trial results with older patients must be interpreted cautiously
    - ~30% of patients in cooperative group trials are >60 years

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

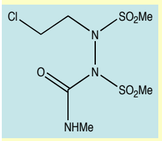
- **Induction Treatment for Elderly AML: Challenges**
  - Leukemia-related risk factors
    - Unfavorable cytogenetics
    - Increased MDR expression
    - Increased secondary AML
  - Patient-related risk factors
    - Age ≥60 years
    - Decreased functional status
    - Medical comorbidities (cardiac, hepatic, pulmonary)
    - Decreased hematopoietic reserves
- **Expected Outcomes in AML Therapy (ECOG Experience 1976-1994)**

Age (yrs)	CR rates (%)	Induction deaths (%)	Drug resistance (%)
≤60	70	10	20
61-69	55	20	25
≥70	35	39	30

- Rates of CR decrease with age:
  - More comorbidities → Increase in induction deaths
  - Worsening biologic factors → Increased drug resistance → poorer responsiveness

Bennett et al. Cancer, 1997;80 (11(suppl): 2205-2209.

CLORETAZINE® PHASE II AML



Cloretazine® (VNP40101M)

- Single agent open label trial
- Cloretazine® 600 mg/m^2 IV over 30-60 min.
- Hydroxyurea 30 mg/kg bid x 6 doses

- 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

OBJECTIVES

- To determine the complete response rate of Cloretazine® in elderly patients with AML or high risk myelodysplasia
- To record the toxicities of Cloretazine® in the study population

ELIGIBILITY

- Age ≥ 60 with AML (excluding M3), or high-risk MDS (IPSS score ≥ 1.5)
- 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
- At least 2 weeks from prior myelosuppressive cytotoxic agents
- No active uncontrolled infection
- No active heart disease including MI within previous 3 months, symptomatic coronary artery disease, uncontrolled arrhythmias or congestive heart failure
- No concurrent disulfiram (Antabuse) or any other standard or investigational treatment for leukemia

RESULTS

Demographics of Study Population	
No. of patients	109
No. treated (evaluable)	107 (106)
Age (median, range)	72 (54-84)
Diagnosis	
de novo AML	44 (42%)
Secondary AML	46 (43%)
High-risk MDS	16 (15%)
Cytogenetics	
Favorable	0
Intermediate (normal, +8, -Y)	58 (56%)
Unfavorable	46 (44%)

Clinical Response		
Diagnosis	**CR/CRp**	**Overall Response (% within group)**
***de novo* AML (44)**	**20/2**	**22 (50%)**
Secondary AML (46)	5/0	5 (11%)
MDS (16)	4/2	6 (38%)
Total (106)	29/4	33 (31%)

RESULTS: *de novo* AML Population

Demographics

No. of Patients	**44**
Age (Median, Range)	**76 (60-88)**
<70	**12 (27%)**
70-79	**32 (52%)**
≥80	**9 (21%)**
Male/Female	**24/20**
Cytogenetics	
Favorable	**0**
Intermediate	**27 (61%)**
Unfavorable	**17 (39%)**
ECOG Performance Status	
PS 0	**8 (18%)**
PS 1	**21 (48%)**
PS 2	**15 (34%)**

Response by Cytogenetics

Clinical Response		
Disease	**CR/CRp**	**Overall Response (% within group)**
***de novo* AML N=44**	**20/2**	**22 (50%)**
Intermediate N=27 (61%)	14/0	14 (52%)
Unfavorable N=17 (39%)	6/2	8 (47%)

Response by Age and PS

	Age 60-69		Age 70+	
	All patients	**Responders**	**All Patients**	**Responders**
PS 0	0 (0%)	0 (0%)	8 (25%)	4 (50%)
PS 1	8 (67%)	5 (63%)	13 (41%)	5 (38%)
PS 2	4 (33%)	2 (50%)	11 (34%)	6 (55%)
Total	12	7 (58%)	32	15 (47%)

RESULTS: *de novo* AML Population (continued)

Distribution of Poor-Risk Factors

# Risk Factors	Overall N (%)	Unfavorable cytogenetics N (%)	PS 2 N (%)	Cardiac Disease N (%)	Pulmonary Disease N (%)	Hepatic Disease N (%)
Age + 0	8 (18%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Age + 1	10 (23%)	2 (20%)	0 (0%)	7 (70%)	1 (10%)	0 (0%)
Age + 2	15 (34%)	8 (55%)	6 (40%)	10 (67%)	2 (13%)	4 (27%)
Age ≥ 3	11 (25%)	7 (64%)	9 (82%)	7 (63%)	6 (54%)	8 (72%)

Response by Number of Risk Factors

# Risk Factors	# patients	CR/CRp	CR/CRp (%)
Age + 0	8(18%)	5	62%
Age + 1	10(23%)	5	50%
Age + 2	15(34%)	5	33%
Age ≥ 3	11(25%)	7	64%
All	44	22	50%

ADVERSE EVENTS (at least possibly related)

	Worst Grade per Patient N=44					
EVENT	**1-2**	**3**	**4**	**5**	**Total N**	**(%)**
Infusion-related symptoms	**25**	**1**	**0**	**0**	**26**	**59%**
Gastrointestinal disorders	**22**	**3**	**0**	**0**	**25**	**57%**
Constitutional symptoms	**10**	**3**	**1**	**0**	**14**	**32%**
Infection including febrile neutropenia	**3**	**4**	**3**	**0**	**10**	**23%**
Neurologic dysfunction	**5**	**2**	**0**	**0**	**7**	**16%**
Non-infectious pulmonary disorders	**3**	**3**	**0**	**0**	**6**	**14%**
Skin/Rash	**4**	**1**	**0**	**0**	**5**	**11%**
Cardiac disorders	**3**	**0**	**1**	**1**	**5**	**11%**
Renal dysfunction	**0**	**1**	**1**	**0**	**2**	**5%**
Metabolic changes	**1**	**1**	**0**	**0**	**2**	**5%**
Hepatic disorders	**0**	**0**	**1**	**0**	**1**	**2%**
Musculoskeletal	**1**	**0**	**0**	**0**	**1**	**2%**
N	**77**	**19**	**7**	**1**	**104**	
%	**74%**	**18%**	**7%**	**1%**	**100%**	

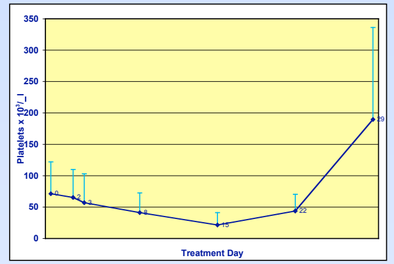
EARLY DEATHS (<30 days)

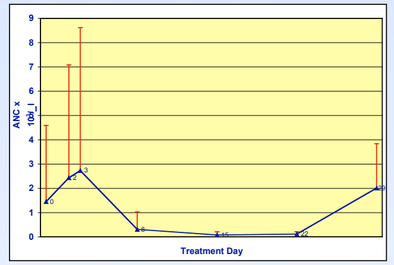
Primary Cause	N=44 (%)
Progressive Leukemia	6
Infection during neutropenia	2
Total	8 (18%)

CONCLUSIONS

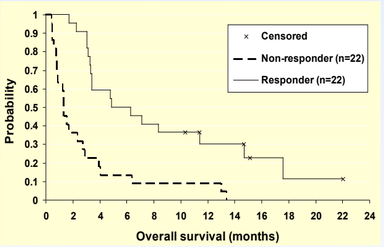
- 50% response to single-agent Cloretazine® in elderly patients (median age 76y) with *de novo* AML
- Cloretazine® was active in patients with high-risk characteristics---unfavorable cytogenetics, declining performance status, and/or medical comorbidities
- Cloretazine® was well tolerated in this group of elderly patients with minimal non-hematologic toxicity

CLORETAZINE® MYELOSUPPRESSION (mean ± SD)





PROBABILITY OF SURVIVAL BY RESPONSE



Responders (N=22)	
Median survival	171 days
Overall survival (OS) at one year	30%
Disease - free survival (DFS) at one year	20%
Non-responders (N=22)	
Median survival	47 days
Overall survival (OS) at one year	5%

FUTURE DIRECTIONS

- A confirmatory Phase II trial in untreated elderly patients (≥60y) with *de novo* poor risk AML is underway