COMORBIDITY DESCRIPTION USING THE HEMATOPOIETIC CELL TRANSPLANTATION-SPECIFIC COMORBIDITY INDEX (HCT-CI) IN ELDERLY *DE NOVO* POOR RISK AML PATIENTS TREATED WITH LAROMUSTINE (ONRIGIN™)

Abstract #7050

G. Schiller[1], S. O'Brien[2], N. Vey[3], A. Pigneux[4], D. DeAngelo[5], J. Karp[6], D. Hudak[7], J. Kell[8], R. Stuart[9], F. Giles[10]

[1]UCLA School of Medicine, Los Angeles, CA; [2]University of Texas MD Anderson Cancer Center, Houston, TX; [3]Institut Paoli Calmettes, Marseille, France; [4]Hopital Haut Leveque, Bordeaux, France; [5]Dana-Farber Cancer Institute, Boston, MA; [6]Sidney Kimmel Cancer Center at Johns Hopkins, Baltimore, MD; [7]Vion Pharmaceuticals, Inc., New Haven, CT; [8]University Hospital of Wales, Cardiff, United Kingdom; [9]Medical University of South Carolina, Charleston, SC; [10]University of Texas Health Science Center, San Antonio, TX

BACKGROUND

ELDERLY AML

- **AML is a disease of an aging population**
  - Increased incidence from 1.7/100,000 at ages 40-44 to 14.8/100,000 at ages 70-74[1]
  - Median age at diagnosis is 68 years[2]
- **Treatment Challenges in Elderly with AML**
  - Leukemia related factors
    - Unfavorable cytogenetics
    - Increased MDR expression
    - Increased Secondary AML
  - Patient related factors
    - Age
    - Poor Performance Status
    - Medical comorbidities
- **Comorbidities in older AML patients often influence treatment decisions and affect treatment outcomes[3-5]**

HEMATOPOIETIC CELL TRANSPLANTATION-SPECIFIC COMORBIDITY INDEX

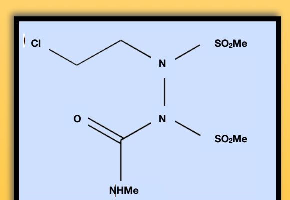
- **Adapted version of the Charlson Comorbidity Index[6,7]**
- **Developed in patients receiving allogeneic SCT (46% had AML or MDS)**
- **HCT-CI scores have been shown to be predictive of early death and survival in patients > 60 years receiving induction therapy for AML:**

TABLE 1: EARLY DEATHS IN 177 AML PATIENTS > 60 YEARS OLD TREATED WITH IDARUBICIN AND ARAC[5]

HCT-CI Score	N (%)	Deaths within 30 days of induction
0	39 (22%)	1 (3%)
1-2	53 (30%)	6 (11%)
≥ 3	85 (48%)	25 (29%)

LAROMUSTINE (ONRIGIN™)*

- **Sulfonylhydrazine alkylating agent**
- **Prodrug activated to**
  - 90CE (1,2 Bis(methylsulfonyl)-1-(2-chloroethyl)hydrazine)
    - Generates cationic chloroethylating species that preferentially targets the O^6 position of guanine
  - Methyl isocyanate
    - Carbamoylating species
    - Inhibits alkylguanine alkyltransferase (AGT), a DNA repair enzyme
- **Active in L1210 cell lines (BCNU, CTX, and melphalan resistant)**
- **Crosses blood-brain barrier**
- **Induces remission as a single agent in Phase I and II leukemia studies[8-10]**



Registered product of
Vion Pharmaceuticals, Inc.
Formerly Cloretazine® (VNP40101M)

METHODS

- **A total of 140 patients were scored for comorbidity by HCT-CI**
  - 85 patients in study CLI-043
  - 55 patients from a retrospectively identified *de novo* subset of study CLI-033 who reasonably met the eligibility criteria for CLI-043
- **Multivariate analysis of comorbidities**
  - Endpoints: response (CR/CRp), overall survival, and 30 day mortality
  - Unadjusted and adjusted (by age, WBC, and cytogenetics) analyses by logistic/Cox regression
  - Comorbidities with frequency > 25% analyzed: cardiac comorbidity, severe pulmonary comorbidity, infection, and arrhythmia
  - 140 patients were included in the unadjusted analysis; 138 patients included in the adjusted analysis (all baseline covariates are required to be present; 2 patients had unknown cytogenetics)

TABLE 2: HCT-CI COMORBIDITY DEFINITIONS[7]

Comorbidity	Definition	Weight
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Cardiac	Coronary artery disease, congestive heart failure, myocardial infarction, or EF ≤ 50%	1
Inflammatory bowel disease	Chronic disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild	Chronic hepatitis, bilirubin > ULN to 1.5 x ULN, or AST/ALT > ULN to 2.5 x ULN	1
Obesity	Patients with a body mass index > 35 kg/m^2	1
Infection	Requiring continuation of antimicrobial treatment after day 0	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	2
Peptic ulcer	Requiring treatment	2
Renal, moderate/severe	Serum creatinine > 2 mg/dL, on dialysis, or prior renal transplantation	2
Pulmonary, moderate	D_LCO and/or FEV_1 66%-80% or dyspnea on slight activity	2
Prior solid tumor	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	3
Heart valve disease	Except mitral valve prolapse	3
Pulmonary, severe	D_LCO and/or FEV_1 ≤ 65% or dyspnea at rest or requiring oxygen	3
Hepatic, moderate/severe	Liver cirrhosis, bilirubin > 1.5 x ULN, or AST/ALT > 2.5 x ULN	3

STUDY OVERVIEW

	CLI-033	CLI-043
Phase	Phase II, open label	Phase II, open label
Enrollment Period	March 2004 - June 2006	May 2006 - August 2007
Patient Population	Prospectively enrolled AML/MDS patients by FAB criteria. Retrospectively identified 55 enrolled patients who were age ≥ 60 years with *de novo* AML by WHO criteria with at least one poor risk factor: • Age ≥ 70 • Unfavorable cytogenetics • ECOG PS 2 • Cardiac, pulmonary, or hepatic dysfunction	Prospectively enrolled 85 patients age ≥ 60 with *de novo* AML by WHO criteria with at least one poor risk factor: • Age ≥ 70 • Unfavorable cytogenetics • ECOG PS 2 • Cardiac, pulmonary, or hepatic dysfunction
Induction	Laromustine 600 mg/m^2*	Laromustine 600 mg/m^2
Consolidation	Laromustine 400 mg/m^2	AraC 400 mg/m^2/day x 5 days
Primary Objective	Complete Response (CR and CRp)	Complete Response (CR and CRp)
Secondary Objectives	Toxicity Spectrum Pharmacokinetics	Progression-free and Leukemia-free survival Overall survival Toxicity Spectrum

**45 of 55 patients also received hydroxyurea 30 mg/kg po q12 h x 6 doses (day 1-3)*

RESULTS

TABLE 3: DEMOGRAPHICS

	N=140
Patients treated	140
Median (range) Age	74 (60-88)
Male	80 (57%)
ECOG PS 0	35 (25%)
ECOG PS 1	54 (39%)
ECOG PS 2	51 (36%)
Intermediate cytogenetics	69 (49%)
Unfavorable cytogenetics	63 (45%)
Median (range) baseline WBC [x10^9/L]	4.7 (0.2-201)

TABLE 4: RESPONSE, EARLY DEATHS, AND OVERALL SURVIVAL BY HCT-CI SCORE

HCT-CI Score	N (%)	CR/CRp	Deaths within 30 days of 1st induction	12 month OS
0	7 (5%)	5 (71%)	0	43%
1-2	20 (14%)	8 (40%)	4 (20%)	13%
≥ 3	113 (81%)	38 (34%)	16 (14%)	21%
Total	140	51 (36%)	20 (14%)	21%

MULTIVARIATE ANALYSIS OF COMORBIDITIES

- Infection predicted for 30 day mortality (unadjusted p=0.045, adjusted p=0.01)
- Severe pulmonary comorbidity was associated with overall survival (unadjusted p=0.02, adjusted p=0.06)
- None of the 4 most common comorbidities with frequency >25% (cardiac, severe pulmonary, infection, arrhythmia) predicted for response

TABLE 5: HCT-CI COMORBIDITIES DISTRIBUTION

HCT-CI Comorbidity	N (%)
Cardiac	59 (42%)
Pulmonary, severe	55 (39%)
Infection	49 (35%)
Arrhythmia	43 (31%)
Psychiatric disturbance	33 (24%)
Diabetes	31 (22%)
Pulmonary, moderate	26 (19%)
Prior solid tumor	26 (19%)
Liver, mild	26 (19%)
Heart valve disease	22 (16%)
Obesity	17 (12%)
Cerebrovascular disease	6 (4%)
Liver, moderate/severe	5 (4%)
Peptic Ulcer	4 (3%)
Rheumatologic	3 (2%)
Renal, moderate/severe	1 (1%)
Inflammatory bowel disease	0

- Median (range) HCT-CI score: 5 (0-12)

CONCLUSIONS

- **The majority (81%) of elderly poor risk AML patients treated with laromustine as induction therapy had a HCT-CI score of ≥ 3, confirming the poor risk nature of this patient group.**
- **The induction death rate for patients with HCT-CI score ≥ 3 treated with laromustine was lower than that reported for a group of patients with HCT-CI score ≥ 3 treated with standard induction chemotherapy (14% vs 29%)[5].**
- **In a multivariate analysis, infection predicted for early death but was not predictive for overall survival. Severe pulmonary comorbidity was associated with overall survival. Adjusting for known prognostic variables in AML (age, WBC, cytogenetics) did not alter these findings.**
- **Laromustine, as a single agent at 600 mg/m^2, produced remissions in 36% of elderly poor risk AML patients enrolled to two phase II studies.**

REFERENCES: 1. Leukemia & Lymphoma Society Facts 2007-2008: Age-Specific Incidence Rates for AML (All Races). 2001-2005. **2.** Appelbaum. *Blood*. 2006. **3.** Kantarjian. *Cancer*. 2006. **4.** Etienne. *Cancer*. 2007. **5.** Giles. *Br J Haematol*. 2007. **6.** Charlson. *J Chronic Dis*. 1987. **7.** Sorror. *Blood*. 2005. **8.** Giles. *Clin Cancer Res*. 2004. **9.** Giles. *JCO*. 2007. **10.** Schiller. ASCO abstract 7026. 2008.