Abstract # 3854

Predictors of Response and Survival in 206 AML Patients Treated with Guadecitabine in a Phase 2 Study

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Background

Guadecitabine is a next generation hypomethylating agent (HMA) resistant to degradation by cytidine deaminase which results in prolonged in vivo exposure to the active metabolite decitabine. We conducted a prospective phase 2 study testing different schedules of guadecitabine in 206 AML patients: 103 Treatment Naïve (TN) AML elderly or unfit for intensive chemotherapy and 103 relapsed/refractory (r/r) AML. We present here the results of multiple logistic regression, and Cox regression analyses of predictors of composite Complete Response or CRc (CR+CRp+CRi) and overall survival (OS).

Methods

Multiple logistic regression analysis of CRc response (CR+CRi+CRp), and Cox regression analysis of Overall Survival (OS) were conducted with inclusion of variables listed in Table 1. Backward elimination method with alpha = 0.05 was used to reach the final model

Table 1. Variables included in the model

Variable Title	Variable Categories Tested
AML Disease State	r/r AML vs TN AML
Guadecitabine Treatment Schedule	10-day vs 5-day
Age	<75 years vs ≥ 75 years
ECOG Performance Status	0-1 vs ≥2
Cytogenetics	Others vs Poor-risk cytogenetics
Baseline BM Blasts [1]	≤40% vs >40%
Baseline PB Blasts [1]	≤30% vs >30%
Baseline Total WBCs [1]	<20,000/µL vs ≥ 20,000/µL
Flt-3 ITD mutation	Present vs Not Detected
NPM mutation	Present vs Not Detected
TP53 mutation	Present vs Not Detected

[1] Cutoff values for BM and PB blasts were based on median and mean number respectively; cutoff for WBCs was used as a standard cutoff of proliferative AML.

RESULTS

206 AML patients were treated in the guadecitabine phase 2 program with the following variables distribution:

Table 2. Variables Distribution

Variable	Categories	N (%)
Disease State	Relapsed/refractory AML	103 (50%)
	Treatment naïve AML	103 (50%)
Age	< 75 Years	115 (56%)
	≥ 75 Years	91 (44%)
Guadecitabine schedule	10-day	105 (51%)
	5-day	101 (49%)
ECOG PS	0-1	153 (74%)
	2-3	53 (26%)
Cytogenetics	Others	121 (59%
	Poor Risk-cytogenetics	85 (41%)

Table 3. Variables Distribution cont.

Variable	Categories	N (%)
Baseline BM Blasts	≤40%	107 (52%)
	>40%	99 (48%)
Baseline PB Blasts	≤30%	138 (68%)
	>30%	65 (32%)
Baseline Total WBCs	<20,000/µL	186 (90%)
	≥ 20,000/µL	20 (10%)
Flt-3 ITD mutation	Present	16 (8%)
	Not Detected	190 (92%)
NPM mutation	Present	19 (9%)
	Not Detected	187 (91%)
TP53 mutation	Present	8 (4%)
	Not Detected	198 (96%)

Table 4. Univariate Logistic Regression Results for Response (All Variables)

Variable	Odds Ratio of Response	P-value
r/r AML vs TN AM	0.26	<.0001
Guadecitabine Schedule (10day vs 5day)	1.15	0.62
AGE (<75 vs ≥75 years)	0.33	0.0002
ECOG PS (0-1 vs 2-3)	1.44	0.28
Cytogenetics (Others vs Poor Risk)	1.14	0.64
BM blasts (≤40% vs >40%)	1.64	0.09
PB blasts (≤30% vs >30%)	2.30	0.01
WBCs (<20,000/µL vs ≥20,000/µL)	1.50	0.42
Flt3-ITD mutations (No vs Positive)	1.40	0.54
NPM mutation (No vs Positive)	0.84	0.72
TP53 mutation (No vs Positive)	1.04	0.96

Table 5. Multiple logistic Regression Results for Response – Final Model (Statistically Significant Variables)

Variable	Odds Ratio of Response (95% CI)	P value
r/r AML vs TN AML	0.22 (0.11 , 0.42)	< 0.0001
ECOG PS 0-1 vs 2-3	2.18 (1.02, 4.64)	0.044
PB Blasts ≤30% vs >30%	2.03 (1.01, 4.06)	0.045

- Multiple logistic regression analysis indicates that TN AML patients have five-fold higher odds of response to guadecitabine (Odds ratio 0 .22) than r/r AML patients, while patients with ECOG PS 0-1 and PB blasts ≤30% have two-fold higher odds of response (odds ratio 2.18 and 2.03) than patients with ECOG PS 2-3 or PB blasts >30%
- The impact of guadecitabine schedule (10 day vs 5 day) analysis is limited by the different effect of the schedule on r/r AML compared to TN AML (10-day treatment produced higher CRc in r/r AML but not in TN AML)

Table 6. Univariate Cox Regression Analysis for Overall Survival (All Variables)

Variable	Hazards Ratio	P value
r/r AML vs TN AML	1.07	0.63
Guadecitabine Schedule (10day vs 5day)	1.02	0.88
AGE (<75 vs ≥75 years)	1.03	0.86
ECOG PS (0-1 vs 2-3)	0.63	0.007
Cytogenetics (Others vs Poor Risk)	0.63	0.003
BM blasts (≤40% vs >40%)	0.63	0.0025
PB blasts (≤30% vs >30%)	0.54	0.0002
WBCs (<20,000/µL vs ≥20,000/µL)	0.65	0.079
Flt3-ITD mutations (No vs Positive)	0.86	0.61
NPM mutation (No vs Positive)	1.21	0.49
TP53 mutation (No vs Positive)	0.66	0.26

Table 7. Multiple Cox Regression Analysis for Overall Survival – Final Model (Statistically Significant Variables)

Variable	Hazards Ratio (95% CI)	P value
ECOG PS 0-1 vs 2-3	0.69 (0.49, 0.97)	0.033
Cytogenetics (Others vs Poor risk)	0.68 (0.50, 0.93)	0.016
PB Blasts ≤30% vs >30%	0.61 (0.44, 0.85)	0.004

- Final multiple Cox Regression Analysis model indicates that patients with ECOG PS 0-1 , patients without poor risk cytogenetics, and patients with baseline PB blasts ≤30% are statistically significant predictors of longer OS while age, disease state, guadecitabine schedule, baseline BM blasts %, total WBCs count, or genetic markers were not statistically significant predictors of OS on guadecitabine treatment
- The impact of genetic markers (Flt-3 ITD, NPM, and TP53) analysis is limited by the relatively small number of patients with these mutations (<10% each)

Summary and Conclusions

- Results of multiple variable regression/Cox analyses of odds of response (CRc), and of OS in 206 AML patients treated in guadecitabine phase 2 program show that:
  - TN AML unfit for intensive chemotherapy have 5-fold higher odds of response than in r/r AML, and that patients with ECOG PS 0-1 and baseline PB blasts ≤30% have two-fold higher odds of response than patients with ECOG PS 2-3 and PB blasts >30%
  - The only statistically significant variables for OS were ECOG PS 0-1, baseline PB blasts ≤30%, and patients without poor risk cytogenetics
- Other known variables such as age, baseline BM blasts %, baseline total WBCs, and genetic markers (Flt-3 ITD, NPM, and TP53) did not significantly impact clinical complete response (CRc), or OS with guadecitabine treatment

Conflict-of-interest statement: Consultancy/advisory board: Kantarjian,Kropf, Issa, O'Connell, Yee, research funding: Roboz,Yee; Astex employment: Hao, Ahanonu, Azab. There are no relationships to disclose for Jabbour, Kropf, Stock, Podoltsev.

Poster presented at: ASH Annual meeting, Atlanta, GA Dec 9 – 12, 2017