SUPPLEMENTARY APPENDIX

Cytogenetic heterogeneity negatively impacts outcomes in patients with acute myeloid leukemia

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 doi:10.3324/haematol.2014.117267
Manuscript received on September 16, 2014. Manuscript accepted on December 17, 2014.
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Outcome definitions and statistical methods

Complete remission (CR) was defined as bone marrow blasts < 5%, the absence of blasts with Auer rods, the absence of extramedullary disease, absolute neutrophil count > 1.0×10^9/L (1000/μL), platelet count > 100×10^9/L (100 000/μL), and independence of red cell transfusions. Overall survival (OS) was measured from the patient's date of entry onto the clinical trial until death from any cause, with observations censored at the date of last contact for patients last known to be alive. Event-free survival (EFS) was defined as the time from patient's date of entry onto the clinical trial until the first of completion of protocol therapy without documentation of CR, relapse from CR, or death from any cause. Patients last known to be alive and in CR were censored at date of last contact. Relapse free survival (RFS) was defined for patients who achieved a CR as the time from date of CR to date of relapse from CR or death from any cause. Patients last known to be alive and in CR were censored at the date of last contact. Wilcox-rank sum test were used to test associations between quantitative covariates and Fisher's exact test was used to test associations between categorical covariates. The Kaplan-Meier method was used to estimate survival curves.[i] Log-rank tests were used to assess differences between survival curves. Cox regression[ii] was used to evaluate the endpoints OS, EFS, and RFS and logistic regression was used to evaluate CR rate. Regression models adjusted for potential confounders including clonal heterogeneity, the quantitative covariates age, white blood cell and platelet counts at presentation, percentage of bone marrow and peripheral blood blasts at diagnosis, and the categorical covariates gender, performance status (PS) (0-1 versus 2+) and karyotypic risk group (unfavorable used as reference). For these analyses, patients with one cytogenetic clone were compared to patients with two or more cytogenetic clones. All P values are 2-sided with a significance level of 0.05.

REFERENCES

[i] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;52(282):457-481.

[ii] Cox DR. Regression models and life-tables (with discussion). J R Stat Soc, Series B 1972;34(2):187-220.

Supplemental Table 1. Logistic regression model demonstrating lack of interaction between clonal heterogeneity and cytogenetic risk group.

	CR Rate			EFS			RFS			OS		
Factors	**OR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Clonal Heterogeneity	0.78	0.5, 1.22	0.27	1.39	1.11, 1.73	0.0037	1.91	1.3, 2.81	<0.001	1.44	1.15, 1.8	0.0016
Karyotype (unfavorable risk used as reference)												
Favorable	5.65	3.31, 9.63	<0.001	0.34	0.26, 0.46	<0.001	0.44	0.3, 0.64	<0.001	0.23	0.16, 0.32	<0.001
Intermediate	1.8	1.06, 3.07	0.031	0.81	0.61, 1.07	0.13	1.03	0.68, 1.56	0.9	0.79	0.59, 1.05	0.1
Unknown	1.69	1.04, 2.74	0.033	0.65	0.5, 0.84	0.0012	0.67	0.44, 1.02	0.063	0.58	0.44, 0.76	<0.001
Karyotype/Clonal heterogeneity interaction												
Favorable	1.3	0.36, 4.67	0.69	0.72	0.37, 1.42	0.34	0.52	0.21, 1.27	0.15	0.88	0.41, 1.87	0.74
Intermediate	1.45	0.28, 7.4	0.66	0.73	0.31, 1.74	0.48	0.67	0.19, 2.34	0.53	0.57	0.22, 1.47	0.25
Unknown	20.8	0.59, 7.26	0.25	0.69	0.35, 1.34	0.27	0.65	0.25, 1.69	0.37	0.51	0.25, 1.07	0.074

Abbreviations: CR: Complete remission; EFS: Event free survival; RFS: Relapse free survival; OS: Overall survival; OR: Odds ratio; HR: Hazard ratio; CI: Confidence interval.