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Effect of Genetic Profiling on Prediction of Therapeutic Resistance and Survival in Adult Acute Myeloid Leukemia

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LETTER TO THE EDITOR

Therapeutic resistance, i.e. failure to achieve complete remission (CR) despite not incurring treatment-related mortality (TRM), or relapse after achieving CR, is the principal cause of failure in acute myeloid leukemia (AML). Many clinical, cytogenetic, and molecular characteristics are strongly associated with resistance.[1] However, using areas under receiver operating curves (AUCs) to quantify their predictive ability in >4,500 younger and older adults with newly diagnosed AML, we recently demonstrated that such data, even when combined, provided only limited ability (AUC <0.8) to predict resistance.[2] Greater ability

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CONFLICT OF INTEREST

The authors declare no competing financial interests.

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(AUC >0.90-0.95) to forecast resistance to standard therapy in individual patients might obviate the need to randomize between standard and investigational treatments, optimize care algorithms, and ultimately benefit patients.

Our previous analysis included molecular data pertaining only to *NPM1* mutations and FLT3/ITDs. At that time, we hypothesized that consideration of mutational data for other genes might improve predictive accuracy. Indeed, by profiling close to 20 genes, Patel *et al*. were able to separate participants of a recent Eastern Cooperative Oncology Group (ECOG) phase 3 trial (E1900) with cytogenetically defined intermediate-risk AML into three subgroups with markedly different outcomes.[3] Here, we investigated the extent to which prediction of resistance and survival can be improved by inclusion of detailed molecular data in the E1900 study cohort. Our study also offered the opportunity to assess whether CD25, a marker that has shown to improve risk classification independent of other established biomarkers in the E1900 cohort, could further improve the accuracy of outcome prediction in individual patients.[4]

E1900 (NCT00049517) was a randomized trial that compared daunorubicin doses of 45 mg/m^2 and 90 mg/m^2 each given days 1-3 together with standard-dose cytarabine in 657 patients aged 17-60 years with newly diagnosed AML.[5] Of these, 398 patients had sufficient material available for complete genetic profiling (see below).[3] Institutional review boards of participating institutions approved all protocols, and patients were treated according to the Declaration of Helsinki.

For our analysis, early death ("treatment-related mortality" [TRM]) was defined as death within 28 days after initiating therapy[6] or study registration, if the date of initiation of therapy was unknown. CR, overall survival (OS), and relapse-free survival (RFS) were defined according to International Working Group recommendations.[7] We used several criteria for the definition of therapeutic resistance: (a) failure to attain CR despite surviving at least 28 days from beginning induction therapy ("primary refractory"); (b) primary refractory or RFS ≤3 months; (c) primary refractory or RFS ≤6 months; and (d) primary refractory or RFS ≤12 months.[2] OS and RFS were estimated using the Kaplan-Meier method. We used logistic and Cox regression analyses to assess the relationship between individual covariates and various measures of resistance or OS: age, gender, white blood cell (WBC) count, platelet count, bone marrow blast percentage, disease type (primary vs. secondary), cytogenetic risk, induction treatment arm (high-dose vs. low-dose daunorubicin), CD25 expression (positive vs. negative),[4] and mutational status in the following genes: *ASXL1*, *CEBPA*, *DNMT3A*, *FLT3*, *IDH1*, *IDH2*, *KIT*, *KRAS*, *MLL*, *NPM1*, *NRAS*, *PHF6*, *PTEN*, *RUNX1*, *TET2*, *TP53*, and *WT1;* none of the patients had mutations in *EZH2* and *HRAS*. The integrated mutational/cytogenetic risk algorithm established by Patel *et al*. was also used.[3] Allogeneic hematopoietic cell transplantation was considered as a time-dependent covariate. For both the multivariable logistic regression and Cox models, we used AUCs (also known as c-statistics) to quantify the ability to predict resistance, with AUC=1 indicating perfect prediction and AUC=0.5 indicating no prediction; AUC values of 0.6-0.7, 0.7-0.8, and 0.8-0.9 are commonly considered as poor, fair, and good, respectively.[2] The relative importance of predictors in the multivariable regression models was evaluated by the value of the partial Wald Chi-squared statistic minus the predictor's degrees of

freedom. Bootstrapping was used to estimate bias-corrected values of AUC.[2, 6] All analyses were performed using R (http://www.r-project.org).

Of the 398 patients who had complete genetic profiling data available, 298 survived at least 28 days and also had data on all other covariates of interest (Supplemental Table 1). 201 of these (67.4%) achieved CR while 97 (32.6%) were primary refractory. 103/297 patients (34.7%) with sufficient follow-up time were either primary refractory or had a RFS of ≤3 months; corresponding figures were 115/296 (38.9%) and 153/295 (51.9%) for being primary refractory or having a RFS of ≤6 months and ≤12 months respectively.

As might be expected, the integrated mutational/cytogenetic risk algorithm, as developed in the E1900 cohort based on genomic profiling data,[3] was the single best predictor of resistance (AUCs ranging between 0.64 and 0.69 across the several definitions of resistance) and survival (AUC of 0.65), followed by cytogenetic risk and *FLT3/NPM1* status (AUCs ranging between 0.59 and 0.64). Bootstrap-corrected "simple" models combining data on cytogenetic risk and clinical factors (age, gender, performance status, white blood cells, platelet counts, marrow blast percentage, and treatment arm) yielded AUCs of 0.69-0.73 for the prediction of primary refractoriness or primary refractoriness/RFS of ≤3, ≤6, or ≤12 months, and an AUC of 0.68 for the prediction of OS (Table 1). Adding *FLT3/NPM1* status to the simple model improved the predictive to about the same extent (2-4%) as when information on all other 15 profiled genes was added to models containing basic clinical information, cytogenetics, and *FLT3/NPM1* mutational status (2-5%). Bootstrap-corrected "maximal" models combining all these covariates yielded AUCs of 0.77-0.80 for the prediction of primary refractoriness or primary refractoriness/RFS of ≤3, ≤6, or ≤12 months, and an AUC of 0.72 for the prediction of OS (Table 1). In these models, in which individual mutations from the genetic profiling were entered as individual factors, cytogenetic risk and *FLT3/NPM1* status remained the most important individual covariates (Figure 1; detailed results of the multivariable regression and Cox models are provided in Supplemental Table 2). The lower AUC for survival probably reflects the more complicated nature of this endpoint. Addition of CD25 expression data, while associated with adverse outcome in the E1900 cohort,[4] did not materially improve the accuracy of these models for the prediction of resistance (AUCs of 0.77-0.81) or OS (AUC 0.73). The relatively limited sample size did not permit separate subset analyses in the 90 mg/m^2 daunorubicin treatment arm.

Our data indicate that genetic profiling increases the accuracy of multivariable models predicting therapeutic resistance or survival in adults <60 years of age with newly diagnosed AML. Adequately-sized cohorts of homogeneously-treated older adults that are equally well characterized molecularly are currently not readily available to test the impact of adding molecular profiling data on the prediction of therapeutic resistance in patients >60 years of age. However, in our previous studies, our prediction models performed relatively similarly for younger and older adults.[2] We therefore speculate that molecular profiling data may also only slightly improve models that aim to predict resistance in AML, although this assumption will need experimental validation.

In our current studies, the magnitude of improvement is roughly the same as that afforded by knowledge of the *FLT3*-ITD/*NPM1* mutation status. Although calculations of statistical

significance are not straightforward for AUCs, such increases are almost certainly "statistically significant". Nevertheless, here, we are less concerned with statistical significance than with the practical ability to predict resistance with relatively standard therapy such as used in E1900. The extent of this ability has implications for decisions as to whether to recommend standard or investigational therapy and for the imperative for randomization. We conclude that despite the incremental improvement in prognostic ability afforded by genetic profiling as done to date, this ability is limited at least relative to "desirable" AUC values of >0.90-0.95. It is plausible that addition of further pre-treatment information, e.g. on epigenetic or miRNA profiles, or more extensive mutational profiling, may be useful.[8, 9] Still, even for extensive mutational data, clonal heterogeneity within as well as between individual patients may matter and limit their usefulness, as different AML subclones may exhibit differential chemotherapy sensitivities, with resistance reflecting emergence of subclones whose importance cannot be determined at initial presentation.[10] We suspect that, more likely, significant increases in AUC may result from integration of information on treatment response such as early disease clearance[11, 12] or persistence of minimal residual disease.[13, 14]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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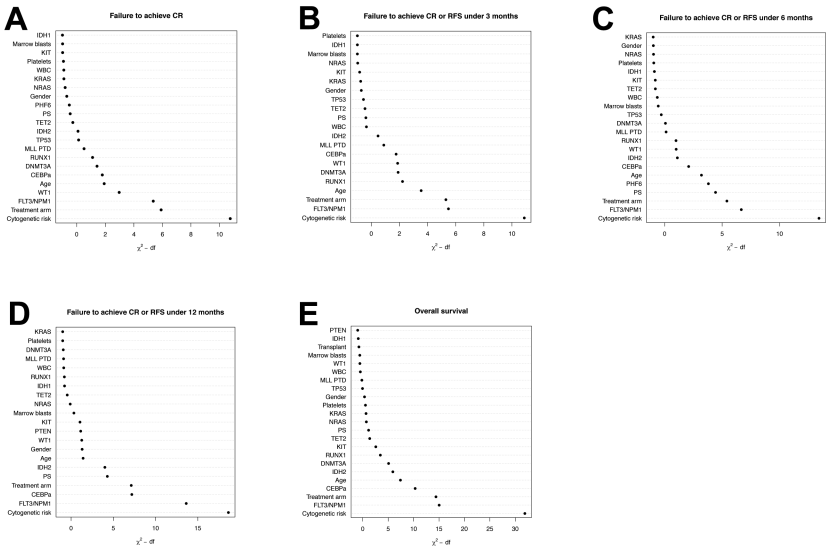

Figure 1. Prediction of Resistance and Survival.

Importance of individual covariates to predict **(A)** failure to attain CR despite surviving at least 28 days from beginning induction therapy (“primary refractoriness”), **(B)** primary refractoriness or relapse-free survival (RFS) ≤3 months, **(C)** primary refractoriness or RFS ≤6 months, **(D)** primary refractoriness or RFS ≤12 months, and **(E)** overall survival using Chi-squared (χ^2) values. “Importance” is evaluated with the Wald χ^2 statistic minus the predictor’s degrees of freedom (df). Covariates with larger χ^2 values are considered more “important” in predicting the outcome of interest. Covariates are listed on the y-axis in order of their χ^2 values, with lowest values at the top and highest values at the bottom.

TABLE 1

Bootstrap-corrected AUCs for various multivariable logistic regression and Cox models

Parameter	*No CR n = 298*	*No CR or RFS ≤3 months n = 297*	*No CR or RFS ≤6 months n = 296*	*No CR or RFS ≤12 months n = 295*	*OS n = 298*
Basic model*	0.64	0.64	0.66	0.66	0.61
Basic model + Cytogenetic risk	0.70	0.69	0.72	0.73	0.68
Basic model + Integrated mutational/ cytogenetic risk schema	0.70	0.70	0.71	0.75	0.69
Basic model + Cytogenetic risk + NPM1, FLT3/ITD	0.73	0.73	0.75	0.76	0.70
Basic model + Cytogenetic risk + NPM1, FLT3/ITD + Other mutations	0.78	0.77	0.79	0.80	0.72
Basic model + Cytogenetic risk + NPM1, FLT3/ITD + Other mutations + CD25	0.78	0.77	0.79	0.81	0.73

*Age, gender, performance status, white blood cell count, platelet count, marrow blast percentage, treatment arm (high-dose *vs.* low-dose daunorubicin)