Empiric definition of eligibility criteria for clinical trials in relapsed/refractory acute myeloid leukemia: analysis of 1,892 patients from HOVON/SAKK and SWOG

Despite incremental progress over the last several decades, adult acute myeloid leukemia (AML) remains difficult to treat, and many patients experience therapeutic resistance, i.e. never attain a complete remission (CR) despite living long enough to have done so (i.e. are "primary refractory") or have their disease relapse after achievement of CR.[1,2] It is well recognized that the likelihood of response to therapy for relapsed/refractory AML and subsequent survival varies greatly across individual patients, with CR rates of 0-70% and 5-year survival rates of 5%-45%. Considerable attention has, therefore, been paid to the assessment of covariates influencing response to salvage therapy in relapsed/refractory AML. The duration of the first CR was identified as primary predictor, but cytogenetics at diagnosis, age, receipt of allogeneic hematopoietic cell transplantation during first CR, and number of prior therapies also play a role.[3-6]

This variability of therapeutic success in relapsed/refractory AML offers a formidable challenge for the conduct of clinical trials for this patient population. One approach would permit inclusion regardless of prior CR duration given the possibility that a new drug might only be effective with longer CR duration, and that even in such patients standard therapies are hardly satisfactory. A second, more common approach, however, relies on CR duration to create a "homogenous" population to facilitate data interpretation; yet, various arbitrary cut-off points have been used for this purpose. Although the close association between duration of previous CR and response to subsequent therapy is widely appreciated, the relationship between primary refractory and relapsed AML is uncertain. Some have argued that these groups fall on a continuum with, for example, the difference between CR durations of 0 (primary refractory) and three months being the same as that between CR durations of three and six months. Others contend that relapsed and primary refractory AML are qualitatively distinct. Twenty-five years ago, Hiddemann *et al*. used a CR duration of less than six months as a criterion defining "refractory AML" based on their analyses of success rates of salvage therapies,[4] but no recent data on this topic are available. Here, we use data from adults with newly diagnosed AML treated on cooperative group trials to examine whether a particular CR duration might be used to define AML trial eligibility based on a relationship with subsequent survival.

Our analyses included data on 1892 adults with newly diagnosed AML (excluding acute promyelocytic leukemia) based on WHO 2008 classification criteria[7] receiving curative-intent treatment on 5 trials conducted by the Dutch-Belgian Cooperative Trial Group for Hematology/Oncology and the Swiss Group for Clinical Cancer Research (HOVON/SAKK; n=1306) or on the SWOG S0106 trial (n=586). Institutional review boards of participating institutions approved all protocols. All patients provided written informed consent for study participation and were treated according to the Declaration of Helsinki.

Based on earlier work, early death was defined as death within 28 days after initiating therapy[8] or study registration if exact date of initiation of therapy was unknown. CR was defined according to international working group recommendations.[1,9] Criteria for failure of initial therapy were completion of induction therapy without CR (CR duration=0) or as relapse from CR. Survival after failure (our principal end point, henceforth referred to as "survival") was measured from the date of completing protocol induction therapy without report of CR or from the date of relapse until the date of death from any cause with patients last known to be alive censored at the date of last contact.

Survival was estimated using the Kaplan-Meier

Table 1. Characteristics of study cohort.

Parameter	HOVON/SAKK n=685	SWOG n=341	All patients n=1,026
Age* [years], median (range)	49 (15-77)	48 (18-60)	49 (15-77)
Patients aged ≥60 years, n. (%)	72 (11)	11 (3)	83 (8)
Male, n. (%)	366 (53)	178 (53)	544 (53)
Cytogenetics n. (%)			
Favorable	49 (7)	29 (9)	78 (8)
Intermediate	372 (54)	146 (43)	518 (50)
Unfavorable	239 (35)	79 (23)	318 (31)
Missing	24 (4)	87 (26)	112 (11)
WBC* [x10^9/L] median (range)	24 (1-400)	13 (0.5-370)	20 (0,5-400
Platelets* [x10^9/L] median (range)	64 (5-998)	55 (2-9300)	62 (2-9300)
Bone marrow blasts* (%)	63 (0-98)	68 (3-100)	61 (0-100)
Performance status*			
0	290 (43)	126 (38)	416 (41)
1	330 (49)	159 (48)	489 (48)
≥2	59 (9)	46 (14)	105 (10)
Missing	6	10	16
CR rate with initial therapy (%)	62	50	58
Survival after failure [months], median	4	10	5

*WBC: white blood cells; CR: complete remission. *At diagnosis.*

Table 2. Cox regression models for survival after failure.

Outcome	Hazard ratios (95% CI) HOVON/SAKK (n=685)	SWOG (n=341)	All patients (n=1,026)	Median survival (95% CI) All patients (n=1,026)
Failed induction*	(Reference)	(Reference)	(Reference)	4 (3-5) months
CR 0-3 months	0.92 (0.69-1.23)	1.70 (0.96-3.02)	1.08 (0.83-1.40)	3 (2-5) months
CR 3-6 months	1.05 (0.83-1.32)	1.67 (1.07-2.62)	1.20 (0.98-1.47)	3 (2-4) months
CR 6-9 months	0.64 (0.51-0.81)	1.25 (0.84-1.87)	0.77 (0.63-0.94)	5 (4-7) months
CR 9-12 months	0.43 (0.31-0.59)	0.88 (0.59-1.30)	0.56 (0.43-0.72)	12 (7-18) months
CR 1-2 years	0.39 (0.30-0.52)	0.55 (0.36-0.83)	0.45 (0.35-0.56)	15 (9-28) months

*Shown are hazard ratios (95% confidence interval). CI: confidence interval; CR: complete remission. *Failed to achieve CR with 1-2 courses of induction chemotherapy.*

method.[10] Cox regression was used to analyze the association between survival and CR duration; the latter was modeled both quantitatively and categorically. Regression analyses that included both cohorts were stratified by cohort. All analyses were performed using R (*http://www.r-project.org*).

Of the 1892 patients, 1026 [54%; median age: 49 years (range: 15-77 years)] failed induction therapy (but did not experience early death; n=430) or had a first CR duration of two years or less (n=596) and were included in our analyses (Table 1). The median survival of the 596 patients with relapsed AML was six months, significantly longer than the median survival of four months of the 430 patients with primary refractory AML (P<001). In the total patient cohort, as well as in the SWOG and HOVON/SAKK cohorts individually, longer CR duration was associated with longer survival (P<0.001). This relationship appeared to be quantitative in both cohorts, i.e. there was no evidence that it changed markedly above or below any specific CR duration cut-off point. However, in the total patient cohort, there was no evidence that the survival for patients with first CR duration of six months or less was different or better than that for patients who were primary refractory to induction therapy (Table 2). The same conclusion could be drawn when analyzing patients treated on the HOVON/SAKK trials as a separate cohort, while in the SWOG cohort, there was no evidence that survival in patients with first CR duration of nine months or less differed from those who were refractory to induction therapy.

Limitations of this work include incomplete information about the therapy received after failure and, particularly, the heterogeneity of patients with relapsed or refractory AML. It is very likely that there is no one single CR duration that is applicable to all patients. Optimally, a system evaluating probability of successful therapy for relapsed or refractory AML would be based on several factors including CR duration, age, cytogenetics, prior treatment, among others. Indeed Breems *et al*. developed such a system.[6] However, it seems that physicians are reluctant to use such systems even when readily available. Therefore, we focused on the simpler task of arriving at an empirical definition of a CR duration that might be used to stratify patients for purposes of clinical trials to replace the arbitrary criteria currently in use. Given the poor prognoses of the vast majority of patients with relapsed/refractory AML, we recognize the value of not limiting entry by CR1 duration. The lower CR rate seen in the SWOG than the HOVON/SAAK cohort is also noteworthy but might reflect the more frequent administration of a second cycle of 7+3 to patients not in CR after a first in patients treated on the HOVON/SAKK trials or differences in the stringency of CR assessment between the cooperative groups. Hence, the use of different criteria for primary refractory AML is another limitation of our work. Nonetheless, assuming survival after failure of initial therapy to be a critical end point in trials of relapsed/refractory AML, our data suggest that patients who are primary refractory to 1-2 courses of intensive induction chemotherapy or who relapse within six months of initial CR have distinctly different survival than patients with CR duration of more than six months. Our findings may inform physicians and patients about expected median survival at the time of induction failure or of first relapse after achievement of CR1. These data may also provide a point of reference for the testing of novel drugs if "historic" comparisons are made. Specifically, although we could not identify any discrete CR1 duration cut-off point, patients with primary refractory AML (CR duration=0) and those who relapse within six months may be considered as homogeneous when included in trials for "relapsed/refractory" AML given similar survival expectations, whereas patients with longer CR1 durations appear distinct with anticipated improved survival estimates. Our findings suggest that the current common practice of dividing relapsed/refractory AML into: a) refractory, b) CR<12 months, and c) CR>12 months is suboptimal. Regardless of whether our 2 subsets are deemed equally eligible for trials, our data could form the basis for a more rational stratification of patients and interpretation of results in trials for relapsed/refractory AML.

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