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Why are there so few randomized trials for patients with primary refractory acute myeloid leukemia?

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A B S T R A C T

Fewer patients with primary refractory AML ("PREF") are entered into phase 3 trials than are patients with relapsed AML. This is particularly noteworthy because data from phase 3 trials for newly diagnosed AML indicated PREF and relapse are equally common. Here I discuss three possible reasons for this discrepancy. First, there is disagreement whether the criterion for PREF AML should be failure of one or two courses of initial induction therapy. Second, there may be an impression that PREF AML is qualitatively worse than relapsed AML. Third, there may be a general unwillingness to randomize patients with such poor prognoses.

Introduction

Patients whose AML fails to respond to initial therapy are often divided into those in whom a remission is not observed ("primary refractory" AML) and those in whom a remission occurs but is transient ("relapsed" AML). Although most relapses occur within 1 year of remission, the rate of relapse remains constant until 3 years from remission date, following which it falls sharply [1]. After 3 years the probability of subsequent relapse is about 5%–10%. Thus patients in remission at 3 years are plausibly considered "potentially cured."

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It is well known most patients with either primary refractory (hereafter PREF) or relapsed AML are unlikely to achieve remission with standard re-induction therapies [2]. *Ipso facto* they become candidates for investigational "salvage" therapies administered on clinical trials. Perusal of several such published trials [3–8] suggests relapsed patients are more often represented than PREF ones (Table 1).

Furthermore, criteria for PREF AML are either not explicit or variable, with failure of one course to produce remission considered sufficient in some studies. The number of PREF patients enrolled in salvage trials seems smaller than might be warranted since several large randomized trials examining therapies for newly diagnosed AML [9–11] suggest the number of PREF patients is similar to the number of relapsed patients (Table 2), bearing in mind PREF AML can be ascertained more quickly than relapsed AML.

Disease criteria unclear

One possible explanation for the underrepresentation of PREF patients is uncertainty as to criteria for PREF AML. Specifically, should these criteria require unresponsiveness to one or two courses of a given initial induction therapy? Othus et al. examined the records of 1505 people who received 7 + 3 on one of five SWOG protocols for initial treatment of newly diagnosed AML [12]. Forty-nine percent attained complete remission (CR) after the first course while 9% died during the first 28 days (early death). Thus 632 patients were alive but not in CR after course 1. Of these patients, 85% had >5% blasts in the most recent post-treatment marrow and blood counts had not reached normal levels in the remainder. Each protocol called for patients not in remission after a first course to receive a second 7 + 3. Nonetheless this occurred in only 53% of patients. The authors found no association between receipt of a second 7 + 3 and either pre-treatment covariates (age, performance status, de novo vs secondary AML, cytogenetics) or post treatment covariates (blast % and % cellularity on first marrow ["day 14"], change in these measurements from baseline, day 14 white blood cell [WBC] count and blood blast%). Only treatment at a Southwest Oncology Group (SWOG) "academic" vs "non-academic" center influenced whether patients received a second 7 + 3, with patients treated at the latter 5.3-fold more likely to do so. This presumably reflects the wider range of therapeutic options available at academic centers. Lest it be thought the administration of a second 7 + 3 to only about 50% of patients who failed a first was peculiar to SWOG, Martin Tallman, MD, former head of the ECOG Leukemia Committee, reported the same phenomenon occurred on the ECOG E1900 study.

The CR rate was 43% among the 632 SWOG patients given a second 7 + 3, while the early death rate was 10%. Unexpectedly, examination of the covariates described in the preceding paragraph failed to indicate any associated with second course CR (Table 3). The same was true considering (a) the day a second 7 + 3 began, (b) patients only with persistent blasts after a first 7 + 3, and (c) each protocol separately. Furthermore, although relapse-free survival and survival were shorter if CR was observed only after a second course, this resulted from the association between courses to CR and "unfavorable" cytogenetics rather than from an independent deleterious effect of two courses to CR.

The similarity in CR and early death rates on a first and a second course of 7 + 3 together with the seeming inability to distinguish who will achieve CR on a second course make administration of a second course to all patients reasonable. Only a trial randomizing between administration of a second 7 + 3 and other therapy can truly address the propriety of these options. The 43% CR rate on a second

Table 1
Representation of primary refractory AML ("PREF") patients in phase 3 trials in relapsed/refractory AML.

Trial	Patients	# PREF Patients	Criteria for PREF
Laromustine [3]	263	0	N/A
Lestaurtinib [4]	224	0	N/A
Clofarabine [5]	320	0–171	?
Lintuzumab [6]	191	86 (45%)	Failed 1–2 courses
Elacytarabine [7]	381	140 (37%)	?
Vosaroxin [8]	711	301 (43%)	AML at day 28

AML, acute myeloid leukemia; PREF, primary refractory AML.