Effect of circulating blasts at time of complete remission on subsequent relapse-free survival time in newly diagnosed AML

Elihu H. Estey, Peter F. Thall, Xuemei Wang, Srdan Verstovsek, Jorge Cortes, and Hagop M. Kantarjian

Introduction

The most widely cited reference specifying criteria for complete remission (CR) in acute myeloblastic leukemia (AML) states that “leukemia blasts should not be present in the peripheral blood.” However, it also notes that “in an occasional patient, a rare blast may be detected in the peripheral blood during marrow regeneration.” Here, we examine whether this equivocation may be replaced by a more definitive statement. At MD Anderson (MDA), we have classified response as complete remission, and have begun postremission therapy, regardless of peripheral blast count, provided that the other criteria for CR are met. Thus, we can analyze whether the presence of peripheral blood blasts (PBBs) in the time of CR-MDA on relapse-free survival (RFS) time. Eighty percent of the 533 patients with newly diagnosed AML or refractory anemia with excess of blasts (RAEB) entering CR-MDA from 1995 to 2000 had no PBBs at time of CR-MDA. Ninety-three percent of the remaining patients, who thus had CR-MDA but not standard CR, had 1% to 5% PBBs at this time. Multivariate analyses, using both conventional and Bayesian approaches, indicated that PBBs had no effect on RFS. For all patients and for the subgroups given and not given granulocyte colony-stimulating factor (G-CSF), the 95% credible interval for the relative risk of failure in the PBB group was nearly centered at 1.0. Thus, our data do not support use of PBBs in defining CR in newly diagnosed AML.

Study design

Patients and methods

Data were derived from all 533 patients with MDA treated for newly diagnosed AML/MDS (myelodysplastic syndrome) between 1995 and 2000 who met our criteria for complete remission. A total of 392 patients (74%) had AML (> 20% blasts in marrow or blood), and the remainder had refractory anemia with excess of blasts (RAEB); patients with acute promyelocytic leukemia (APL) were excluded. We considered a patient to be in complete remission if, after treatment, the marrow had less than 5% blasts (with no Auer rods), extramedullary AML was absent, the platelet count was at least 100 000, and the neutrophil count at least 1000. Patients satisfying our definition of complete remission (CR-MDA, defined as occurring on the day the listed criteria pertained) thus consist of (1) patients meeting conventional criteria for CR and (2) patients meeting all conventional criteria with the exception that they had PBBs; we will refer to the former patients as the CR group and to the latter as the CRB group.

To assess the effects of PBBs and other covariates (Table 1) on RFS time multivariate analyses were conducted. Because use of granulocyte colony-stimulating factor (G-CSF) might determine whether PBBs were present at CR, we did separate analyses of the effect of CRB versus CR on RFS time in patients treated with and without G-CSF during remission induction. It was not possible to ascertain retrospectively whether, and if so for how long, patients received G-CSF. Therefore, we used intent to treat as the indicator of treatment with G-CSF, with patients considered to have received G-CSF if they were treated on a protocol specifying use of G-CSF.

Statistical methods

Kaplan-Meier plots were used to estimate, and log-rank tests to compare, RFS within various patient subgroups. We assessed the ability of patient characteristics or treatment to predict the hazard of relapse or death (failure) using a Bayesian Weibull survival time regression model. Uninformative priors were assumed for all parameters. All computations of posterior distributions were carried out in BUGS 0.5. Variable selection was done in a step-down fashion, dropping at most one variable at a time; all variables were subject to being dropped, with the exception that the indicator of CRB, denoting that the patient satisfied the CR-MDA but not the conventional CR criterion, was kept in the model throughout, as was the indicator for treatment (Table 1). At each step, that variable whose posterior probability of a positive (or negative) effect on RFS time was between 0.10 and 0.90 and closest to 0.50 was dropped, and the model was refit, with this refit repeated until each remaining variable had posterior probability either more than 0.90 or less than 0.10. As a basis for comparison, the corresponding conventional Cox proportional hazards regression model was also fit. Approval was obtained from the University of Texas MD Anderson Cancer Center institutional review board for these studies. Informed consent was provided according to the Declaration of Helsinki.

From the Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; and Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX.


Reprints: Elihu H. Estey, The University of Texas MD Anderson Cancer Center, Department of Leukemia, 1515 Holcombe Blvd, Box 428, Houston, TX 77030; e-mail: ehestey@mdanderson.org.

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Results and discussion

Of the 533 patients 427 (80%) had no PBBs at CR-MDA, and 93% of the remaining 106 patients had 1% to 4% PBBs. The CRB group was younger and presented de novo more often than the CR group. Otherwise, the groups were similar, except that 66% of the CRB group versus 53% of the CR group received G-CSF (P = .02) and time to CR-MDA was shorter in the CRB group (P < .0001, medians of 27 versus 31 days).

RFS was slightly longer in patients with PBBs (Figure 1) and appeared unaffected by the percentage of PBBs (1% versus 2%, etc); the patient with the highest blast count (14%) at CR-MDA has remained in CR for 88 weeks. These results, together with the relatively small size of the entire CRB group, prompted us to focus on RFS on CR versus CR. We note that interpretation of Figure 1 may be biased, given the method we used to date onset of CR-MDA. Specifically, if patients in the CRB group often entered the CR group, the former group’s RFS time would be overestimated by the time needed to move from the former group to the latter. Because we began postremission therapy when CR-MDA was observed, regardless of the PBB count on that day, we cannot ascertain how often patients in the CRB group would have entered the CR group with further observation. The shorter time needed to reach CRB suggests that with further observation patients in this group might well have entered the CR group. However, the median difference in time to CR-MDA between the 2 groups was only 4 days, whereas the time scale for Figure 1 is years.

The conclusion that type of complete remission (CRB versus CR) has little effect on RFS probability was strongly supported by the Bayesian regression analysis (Table 1, columns 1-4). After accounting for the indicated covariates, the posterior probability that CRB was associated with shorter RFS than CR was 0.43. The corresponding fitted conventional Cox model (Table 1, columns 5-6) agreed with the Bayesian model; in particular, after accounting for patient prognostic covariates and treatment, there was no evidence that RFS was affected by whether a patient was in the CRB group rather than the CR group (P = .94). In patients given G-CSF, the posterior probability that CRB was associated with a shorter RFS time was 0.34 and the 95% credible interval for the relative risk of failure with CRB versus CR was 0.65, 1.26. The analogous posterior probability in patients not given G-CSF was 0.75, with 95% credible interval for relative risk (RR) 0.76, 1.67. Thus, although the observation of a favorable effect of G-CSF on RFS (Table 1) may be problematic, it has little effect on our fundamental conclusion. Finally, neither analysis suggested that the effect of CRB varied according to either treatment (TA, FA, IA, Table 1) or diagnosis (AML versus RAEB).

Because this is a retrospective study, we do not know whether the PBBs seen in the CRB group were derived from normal or leukemic precursors. Although this derivation is undoubtedly of interest, our primary purpose is to present data suggesting that the absence of circulating blasts should not be a criterion for CR in newly diagnosed AML. An important therapeutic implication of this conclusion is that the presence of circulating blasts when other criteria for CR are met should not delay the start of postremission therapy.

Table 1. Regression models for RFS

<table>
<thead>
<tr>
<th>Covariate*</th>
<th>Bayesian Weibull model</th>
<th>Cox model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean posterior effect (SD)</td>
<td>95% posterior credible interval for the effect†</td>
</tr>
<tr>
<td>CRB</td>
<td>−0.02 (0.13)</td>
<td>−0.28,0.23</td>
</tr>
<tr>
<td>No G-CSF</td>
<td>0.22 (0.10)</td>
<td>0.01,0.42</td>
</tr>
<tr>
<td>Inv16 or t(8:21)</td>
<td>−0.47 (0.21)</td>
<td>−0.88,0.07</td>
</tr>
<tr>
<td>Cyto genetics −5/−7</td>
<td>0.75 (0.12)</td>
<td>0.53,0.97</td>
</tr>
<tr>
<td>Log [WBC] × (% circulating blasts at presentation)]</td>
<td>0.04 (0.02)</td>
<td>0.01,0.07</td>
</tr>
<tr>
<td>Log days to CR-MDA</td>
<td>0.66 (0.16)</td>
<td>0.35,0.96</td>
</tr>
<tr>
<td>Received TA†</td>
<td>0.26 (0.13)</td>
<td>0.02,0.53</td>
</tr>
<tr>
<td>Received FA‡</td>
<td>0.09 (0.14)</td>
<td>−0.16,0.37</td>
</tr>
</tbody>
</table>

*Age, antecedent hematologic disorder (AHD) of more than 1 month (yes vs no), diagnosis (AML vs RAEB), platelet count, hemoglobin, circulating blast and neutrophil percentages/counts both before treatment and at CR, pretreatment marrow blast percentage, and number of courses of chemotherapy were also considered but dropped from the model.

†Under the Bayesian model, a posterior mean of 0 corresponds to a beneficial and a harmful effect being equally likely. Because the 95% posterior credible interval for the effect of CRB versus CR (−0.28, 0.23) is very nearly centered at 0, there is very weak evidence for either a beneficial or a harmful effect on RFS. Because an effect of 0 corresponds to a relative risk (RR) of 1, each estimated mean and 95% credible interval may be converted to a RR by simply exponentiating. Thus, the RR of failure because of CRB versus CR has 95% credible interval of 0.76, 1.26.

‡A posterior probability of shorter (or longer) RFS close to either 0 or 1 under the Bayesian model corresponds to a small P under the conventional Cox model.

§TA indicates topotecan + ara-C-containing regimen; FA, fludarabine + ara-C-containing regimen. TA and FA were compared with idarubicin + ara-C-containing regimens (IA).
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