Predicting Complete Cytogenetic Response in Chronic Myelogenous Leukemia Patients Treated With Recombinant Interferon α

To the Editor:

Following the report recently published by Ozer et al., we would like to briefly summarize our own experience and add some comments.

In our institution, we have treated with interferon α (IFNa) 52 patients with newly diagnosed chronic myelogenous leukemia (CML). The main characteristics of the patients are summarized in Table 1 and seem to be similar to those of the CALGB study population. The patients were treated with IFNa alone (5 × 10^6 U/m²/day, subcutaneously) after a median interval of 45 days from diagnosis. Forty-two patients (80.7%) achieved a complete hematologic response 3 months after starting IFNa (CHR, Houston criteria). A partial hematologic response was achieved in 9 patients; only 1 patient did not respond. Among the 47 responder patients who had a cytogenetic evaluation, 20 patients achieved a complete cytogenetic response (CCR; 100% Ph-negative metaphases). The median time to CCR was 17 months. Three other patients achieved a major cytogenetic response (> 65% negative Ph metaphases). All the latter patients who achieved a major cytogenetic response (MCR; n = 23)
CORRESPONDENCE

The log rank test). Patients (cumulative incidences and cytogenetic responses were analyzed by the Kaplan and Meier method and were compared using the log rank test).

Table 1. Characteristics of Patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>Our Study</th>
<th>CALGB1</th>
<th>Italian Cooperative Study2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>51 (16-68)</td>
<td>44 (17-79)</td>
<td>47 (± 14)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>31/21 (60%/40%)</td>
<td>61/51 (54%/46%)</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Sokal classification</td>
<td></td>
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<tr>
<td>Low risk</td>
<td>24 (44%)</td>
<td></td>
<td>93 (43%)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>19 (36%)</td>
<td></td>
<td>72 (33%)</td>
</tr>
<tr>
<td>High risk</td>
<td>9 (18%)</td>
<td></td>
<td>52 (24%)</td>
</tr>
</tbody>
</table>

are still alive without transformation; only 2 of them had a cytogenetic relapse. First, these results are similar to those reported by Talpaz et al and seem to be better than those reported by either Ozer et al or the Italian cooperative study group on CML. The differences in the results are not really related to differences in the proportion of patients who presented with bad prognostic factors. According to Sokal et al's classification, most of our patients (82%) belonged to the good and intermediate risk groups, but a similar proportion was observed in the Italian studies (Table 1). In the latter studies, the starting dose of IFNα was 3 to 4 x 10^6 U/m2/d lower than that used in the Houston and CALGB studies or in our own study. In the CALGB study, many patients had a significant dose reduction (64%). Thus, we feel that the differences in the results of the latter studies could be due to differences in the dose of IFN administered. Interestingly, the highest doses of IFN were used in the two single-center studies (Houston study and our study) as opposed to the three other studies that were multicentric (and used lower doses of IFN).

Secondly, Ozer et al strongly criticize the method used by Talpaz et al, who concluded that responders have a longer survival than do nonresponders. Indeed, using the landmark analysis (instead of the Kaplan Meier method), they do not find a significant correlation between cytogenetic response and remission duration or survival. They claim that a prospective study is necessary to answer this question. Such a study has been performed by the Italian cooperative study group on CML, showing that the survival of patients treated with IFN was significantly longer than the survival of hydroxyurea-treated patients. In the latter series, the patients who achieved MCR had the longest survival. In view these results and our own results (because we did not observe transformation in patients with a MCR), we analyzed the factors that could predict the occurrence of a major cytogenetic response and thus identify long-term survivors. Among the 47 patients with cytogenetic analysis, we found that the actuarial incidence of MCR at 3 years was 49% (Fig 1). By univariate analysis, two disease-related variables were found to influence the MCR rate in the 40 evaluable CHR patients: spleen size at diagnosis (P = .088) and peripheral blood blast percentage (P = .066). However, the most significant factor was the achievement of CHR within 3 months (P < .0004). The MCR rate of patients who achieved CHR at 3 months was 82.3%, whereas it was only 29% for patients who did not achieve CHR within 3 months after starting IFN (Fig 2).

For patients who do not achieve an MCR, alternative treatments have to be proposed. Allogeneic bone marrow transplantation (AlloBMT) is only possible for patients less than 45 years of age with an HLA-identical sibling or unrelated donor. Autologous stem cell transplantation (ASCT) could be an alternate treatment. Because some studies have shown that the survival of patients undergoing AlloBMT are negatively influenced by a long interval between diagnosis and AlloBMT and have proposed ASCT or AlloBMT before transplantation, we think that it could be very useful to identify early the patients who will not respond to IFNα. In our study, the CHR rate at 3 months is the best prognostic factor. We are interested in knowing whether this factor could predict the cytogenetic response in other studies, such as the CALGB study.

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Fig 1. Cumulative incidence of MCR among the 47 evaluable patients (cumulative incidences and cytogenetic responses were analyzed by the Kaplan and Meier method and were compared using the log rank test).

Fig 2. Cumulative incidence of MCR among the patients who obtained a CHR in 3 months and the other patients (cumulative incidences and cytogenetic responses were analyzed by the Kaplan and Meier method and were compared using the log rank test, and a multivariate analysis of prognostic factors was performed according to the Cox model).
REFERENCES


RESPONSE

We appreciate the letter by Mahon et al to our report.

Their observations regarding our data, as well as those of other published trials and their own data, help to confirm the nature of the cytogenetic remissions that occur in CML chronic-phase patients after the institution of IFNα therapy. Their data are derived from a single institution trial of 52 patients, which represents an adequate number for comparison, but is distinct in being a homogenous single-institution data set similar to that from the MD Anderson group. In Mahon et al’s analysis, the patient characteristics are similar among their cohort, the Italian Cooperative Study Group cohort, and our own data. Although Sokal criteria were not applied at diagnosis in the CALGB study, one can assume that these newly diagnosed patients with chronic-phase CML are largely similar in characteristics to those of the French group or the Italian Cooperative Study.

In evaluating their data, Mahon makes the following observations:

(1) The cytogenetic response proportions in the French and MD Anderson experience appear to be slightly higher than either the CALGB results or the Italian Cooperative Study Group. We would agree that these slight differences are probably not due to differences in prognostic factors or patient populations. Given that both the CALGB and Italian Cooperative Study Group data are from multi-institutional trials with occasional varying individual investigator criteria for IFN dose reduction and reinstitution, it seems reasonable to conclude that the total delivered dose of IFN may have some impact on either clinical or cytogenetic responses. Whether this translates to a survival difference or not remains to be determined. Mahon et al do not mention the median duration of follow-up which, at the time of publication, was approximately 65 months in the CALGB study.

(2) Mahon et al’s second point concerns the methodology for assessing the relationship between the attainment of a cytogenetic response and subsequent clinical outcome (remission duration and survival). The landmark analysis attempts to deal with the time-dependent nature of the cytogenetic response, but it is definitely not used “instead of the Kaplan-Meier method.” In fact, the landmark analysis compares the distributions of remission duration and survival, estimated by the standard Kaplan-Meier procedure, but restricting attention to those patients still under follow-up at the landmark time point classified into the appropriate cytogenetic response category (ie, cytogenetic responder or not) at that time. Other analyses, such as the modelling approach noted in our report could also be used, but the important point is that any analysis that ignores the time required to attain a cytogenetic response will be seriously biased and produce highly misleading estimates of the true effect of a cytogenetic response. One such naive approach that we were criticizing in our report is the simple comparison of cytogenetic responders and nonresponders ignoring the variable times at which the responses occurred. It should be noted that lack of statistical significance does not mean that there is no effect but that the effect, if present, could not be detected in a study of this magnitude. Finally, the presence or absence of an effect of cytogenetic response on clinical outcome implies nothing about the efficacy of the treatment regimen. Randomized trials such as the one performed by the Italian Cooperative Study Group are the best way to address this issue.

(3) Mahon et al’s third and final point has to do with whether or not surrogate endpoints can be identified that predict for either major cytogenetic responses or for survival, thus permitting alternative therapeutic options for patients who may fail to achieve these endpoints. In their study, complete hematologic response was identified as the best predictor of those patients subsequently achieving a major cytogenetic response.

In the CALGB trial, all patients who underwent cytogenetic analysis had, by definition, achieved a complete hematologic response given that we only began performing cytogenetic follow-up analysis when the peripheral counts had normalized. It does appear evident from the cited publications that those patients obtaining a more rapid hematologic response or, better yet, a rapid cytogenetic response with normalization occurring within 3 months, are most likely to remain Philadelphia chromosome-negative for an extended follow-up period and enjoy prolonged survival.

Patients most likely to benefit from continued IFN therapy are, therefore, those who rapidly normalize their peripheral blood counts and have major reductions in Philadelphia chromosome-positive clones in the bone marrow within a 3- to 6-month timeframe. Patients failing to respond with a major hematologic and cytogenetic response within 12 to 18 months should clearly be considered for alternative therapy, if available. It remains to be determined whether the subset of patients who fall between these two subpopulations should be offered alternative therapy such as autologous bone marrow transplantation. Further follow-up of the Italian Cooperative Study Group randomized patient populations may help to clarify this issue.

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Different origin of nt 1246 glucose-6-phosphate dehydrogenase mutation [letter; comment]

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