Randomized Comparison of Interferon-α, Hydroxyurea, and Busulfan in Chronic Myeloid Leukemia: Response to Kantarjian and Talpaz and to Tura and Baccarani

We appreciate the letters by Kantarjian and Talpaz and by Tura and Baccarani regarding our report.1

Kantarjian and Talpaz compare their retrospective study on 274 interferon-α (IFN)-treated chronic myeloid leukemia (CML) patients2 with the IFN arm of our randomized prospective study that compares IFN with hydroxyurea and busulfan. Although the quality of the group’s studies is acknowledged, it cannot be expected that a randomized study with defined inclusion criteria that follows the intention-to-treat principle will yield identical results. The goal of our study was to analyze the impact of IFN on the duration of the chronic phase and on survival in newly diagnosed chronic-phase CML requiring treatment as compared with standard busulfan or hydroxyurea. There were almost no entry restrictions, particularly no age limits (our oldest patient was 85 years at diagnosis), to obtain information on the true benefit of the respective therapies in a nonpreselected patient population representative of general hematologic practice. In addition, it should be noted that our protocol required monotherapies. In consideration of these differences it is not surprising that Kantarjian and Talpaz’ patient population contains almost twice as many low-risk patients as our patient population and much fewer intermediate- and high-risk patients (Table 1). This difference correlates with a median age of 41 years in the Houston patients as compared with 47.4 years in our patients.

Kantarjian and Talpaz note that only 31% of our patients attained complete hematologic responses as compared with 80% in their group. However, the rates of complete and partial hematologic responses together are similar in both studies (83% in our patients and 87% in the Houston patients) despite the differences in patient group

### Table 1. Risk Profiles of Patient Populations According to Sokal

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>German Group (n = 139)</th>
<th>Kantarjian/Talpaz (n = 237)</th>
<th>Italian Group (n = 218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (%)</td>
<td>27</td>
<td>52</td>
<td>43</td>
</tr>
<tr>
<td>Intermediate (%)</td>
<td>35</td>
<td>25</td>
<td>33</td>
</tr>
<tr>
<td>High (%)</td>
<td>38</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>Ratio of low-to-high-risk patients</td>
<td>0.71</td>
<td>2.26</td>
<td>1.79</td>
</tr>
</tbody>
</table>
composition. This good response rate was achieved although the no-
response group, because of the intention-to-treat principle in random-
ized studies, comprised 6 patients who never received IFN. However,
minor differences in definition and procedures may cause major
differences in response rates. Looking at the definitions of complete
hematologic response, we noted that the Houston group required a
normal differential with no blasts, promyelocytes, or myelocytes. Our
definition also requires the absence of metamyelocytes, unless
bands and metamyelocytes together are 5% or less.

Furthermore, because almost one half of the Houston patients
received IFN in combination with other drugs such as hydroxyurea
or IFN γ, which are known to influence the degree of hematologic
response, a higher complete hematologic remission rate had to be
expected. The combination of IFN with hydroxyurea or similar drugs
would have been a protocol violation in our study. Preliminary data
of an ongoing study of our group that analyzes the combination of
IFN and hydroxyurea show that the rate of complete hematologic
remissions is indeed much higher (58% by now).

We agree with the concept that achieving minimal tumor burden
in CML prolongs survival as discussed by us previously in the
context of lower white blood cell (WBC) counts obtained with hy-
droxyurea. However, the observation of more cytogenetic responses
in the Houston patients is in line with the considerations that good-
risk patients are more likely to obtain cytogenetic responses than
intermediate- and high-risk ones and that the likelihood of detecting
transient responses increases with the frequency of analyses.

The second question of Kantarjian and Talpaz applies only in
part, because we consider the overall hematologic response rates to
be similar in the two studies. Although there was a learning period
for participating physicians in the initial phase of the study, this
period should not be overestimated, because the German study group
has more than 20 years of expertise in performing cooperative studies
(overall protocol violation rate only 10.5%). In the remaining 90% of
patients the dosage of IFN depended on hematologic response
(goal: WBC counts of 2 to 4 × 10^9/L) and tolerability. The mean
daily IFN dosage in our study was close to 5 × 10^6 IU/m^2 during
the first 3 months, declined to about 3.5 × 10^6 IU/m^2 by 12 months,
and was 3 × 10^6 IU/m^2 at 30 months. This is not much less than in
the Italian study (as opposed to what Kantarjian and Talpaz state in
their letter), which reports 4.28 × 10^6 IU/m^2 during the first 14
months and, at least in cytogenetic nonresponders, considerably
lower dosages thereafter. The majority of our patients reached and
maintained low WBC counts under increasingly lower IFN doses.
These data are compatible with the possibility that the tolerability of
high doses of IFN is less in intermediate- and high-risk patients.
We therefore would agree with Kantarjian and Talpaz’ assumption
that different patient characteristics are an important reason for dif-
f erences in results.

Concerning questions 3, 4, and 5, we agree that the frequency of
cytogenetic analyses is of relevance for the recognition of cytoge-
genetic responses. It therefore had to be expected that our lower fre-
quency of cytogenetic analyses (half the frequency requested by our
protocol) would recognize fewer cytogenetic responses. It has to be
critically asked how useful a method really is that requires consid-
erable effort and has to rely on single responses, as transient as they
may be. Hematologic response probably is the better marker, as we
and others have shown. We would expect that a truly relevant
response is longer lasting and detectable by less frequent analyses
than requested by Kantarjian and Talpaz. However, we do agree,
and stated so in our report, that, due to the low frequency of our
cytogenetic follow-up analyses, we might have missed transient cy-
togenetic responses and that this may be a major reason for our
lower cytogenetic response rate. We also agree that the inclusion of
unrecognized transient cytogenetic responders in the no-response
category might falsely improve the survival outcome of nonrespon-

derers as compared with responders. It might indeed be that after pro-
longed observation of our patient group those with major or complete
cytogenetic responses may have a relevant survival advantage, as
stated in our report.

However, we would not agree that the nonrecognition of cyto-
genetic responders as a consequence of fewer cytogenetic analyses has
any impact on survival, because the median survival of our IFN-
treated patients compares favorably with that of other published
series (Table 2). As of January 20, 1995, the median survival had not
been reached at 94 months in our low-risk IFN-treated patients
(n = 30) and is 47 months in our high-risk patients (n = 50), similar
to the data shown by Kantarjian and Talpaz in their Table 2. We
therefore conclude that the differences in overall survival are primar-
ily caused by the patient group composition (ratio of low- to
high-risk patients, Table 1).

We agree with Tura and Baccarani that there are several important
differences between the German and Italian studies. We would first
like to comment on the inclusion criteria.

Although our inclusion criteria are different from the Italian ones
(no age limit and only patients requiring treatment were randomized),
chronic phase was a requirement. Five (of 513) randomized patients
(2 in the IFN arm) were found to have accelerated or blast phase
after randomization (as mentioned in our report) and were included
in the intention-to-treat evaluation.

We believe that three further objective differences between the
Italian and German studies contributed to the different outcome
and should be mentioned. First, our study protocol prohibited the
combination of IFN with hydroxyurea as practiced in the Italian
study, because strictly monotherapies were compared. The inclusion
of hydroxyurea in the treatment schedule of our study might have
allowed the continuation of IFN in a higher percentage of our pa-

tients. Preliminary results of our study on the combination of IFN
and hydroxyurea confirm this assumption. The second difference
that possibly, at least in part, results from the different inclusion
criteria is the patient group composition. The proportion of low-risk
patients of the Italian study is (similar to the Houston study) much
higher than that of the German study (Table 1). The third difference
is the treatment schedule in the hydroxyurea control arm. In our
study, hydroxyurea was administered in a dosage sufficient to reach
normal WBC counts, resulting in a lower tumor burden. As a conse-
quence, our hydroxyurea-treated patients have a longer median sur-


vival (56 vs 52 months) despite their much less favorable risk profile.
In addition to the difference in patient group composition, we con-
side r the good median survival time of our hydroxyurea-treated pa-
tients essential for not obtaining a significant survival difference
between IFN and hydroxyurea, also because the median survival of
our IFN-treated patients is not significantly different from that of

other series (Table 2), including the Italian patients (the Italian sur-
vival curve is within the 95% confidence intervals of our survival
curve).

Finally, in looking at all three studies and the impact of IFN
dosage on cytogenetic response and long-time CML-free survival it

Table 2. Median Survival Times of IFN-Treated CML Patients

| Table 2. Median Survival Times of IFN-Treated CML Patients |
|-------------------|-------------------|
|                   | Months |
| Talarz et al² (n = 93) | 62     |
| Kloke et al² (n = 71)  | 55     |
| Ozer et al³ (n = 107)  | 66     |
| Italian Group³ (n = 218) | 72     |
| Hehlimann et al³ (n = 133) | 66     |

From www.bloodjournal.org by guest on August 30, 2017. For personal use only.
has to be kept in mind that the optimal IFN dosage in CML is still controversially discussed. Since the discussion of this topic at the 1992 annual meeting of the German CML Study Group, no controlled comparison of IFN dosages that would clarify the matter has been published.

R. Hehlmann
H. Heimpel
J. Hasford
The German CML Study Group
III. Medizinische Klinik
Klinikum Mannheim
Universität Heidelberg
Mannheim, Germany

REFERENCES


Randomized Comparison of Interferon-α, Hydroxyurea, and Busulfan in Chronic Myeloid Leukemia: Response to Kantarjian and Talpaz and to Tura and Baccarani

R. Hehlmann, H. Heimpel and J. Hasford