Among the 20 patients with complex aberrations, 11 karyotypes contained a chromosome 7 abnormality (also mostly monosomy 7). Four of 11 patients with complex karyotype including aberrations of chromosome 7 showed cytogenetic responses (Figure 1; Table 1) compared with 2 responders of 9 patients with complex karyotype not containing a chromosome 7 abnormality. This high response rate in patients with chromosome 7 abnormalities is in stark contrast to the notoriously low response rate of MDS patients receiving conventional low-dose therapy with AraC.4

In summary, the optimal dose and schedule of DAC for a nonintensive, outpatient treatment of high-risk MDS patients may not yet be defined. The Bayesian design has not been uniformly accepted as the optimal methodology to identify treatment superiority.5 Systematic evaluation of cytogenetic responses in different cytogenetic subgroups of MDS and acute myeloid leukemia will continue to be a very valuable and robust surrogate parameter to compare efficiency of azanucleoside schedules6 and other novel agents7 used to treat MDS.

Björn Rüter, Pierre Wijermans, Rainer Claus, Regina Kunzmann, and Michael Lübbert

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References


To the editor:

Decitabine dosage in myelodysplastic syndromes

I read with interest the recent publication of Kantarjian and colleagues1 regarding decitabine schedules in higher-risk myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML).

The authors conclude that the 5-day intravenous decitabine schedule had a higher response rate than the other tested schedules. This study is important, because there is considerable uncertainty about the optimal dosing, and the suggestion that one schedule is superior to another may have implications for the use and the reimbursement of the substance. However, the probability that the reported superiority of the 5-day intravenous schedule over the others is merely a chance finding is considerable. First, the Bayesian randomization method used in this trial assigned a patient to a treatment arm according to the estimates of the probability that the complete remission (CR) rate of the schedule was superior to the other 2 schedules. This happened after 15 patients had been assigned to each of the treatment arms. The number of patients achieving CR according to the article was as shown in Table 1 (lines 1 and 2). Line 3 assumes the final response rate (39%) in the superior group also occurred in the first 15 patients. However, these observed differences could occur by chance alone, and it is difficult to understand why more patients should be randomized to schedule 1 at that moment.

There is, however, a second reason why we should be cautious in readily accepting the reported findings. The probability that a study finding is correct is not only a function of the P value and the power of a study. It also very much depends on the a priori probability that the question under investigation is sensible,2 for example, the a priori probability that the investigators had a good idea regarding their study testing different decitabine dosages. If the idea under investigation (eg, intravenous schedule superior to subcutaneous schedule) has a 10% chance to be correct and the study result yields a P = .05 at a power of 80%, the probability of this “statistically significant result” being false positive is 36%2. There is no mathematic or statistical approach to the measurement of a priori probabilities. Now, it is beyond any doubt that Kantarjian and coworkers are experts in the field of the MDS. Indeed, I would not hesitate to refer to them if I had any question regarding any aspect of this disease. Still, as long as we are making intelligent guesses as to the exact mechanism of action of decitabine, the a priori probability that 3 different dosing schedules with the same cumulative dose are significantly different in terms of efficacy, is at least debatable, even after contemplating the results of this study.

Therefore, the data presented are not sufficient to allow final conclusions on the optimal dosage of decitabine in MDS. In the

<table>
<thead>
<tr>
<th>Table 1. Decitabine dosage and response rates in patient subgroups</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>No. of patients 64</td>
</tr>
<tr>
<td>No. of patients in CR (%)</td>
</tr>
<tr>
<td>(Estimated) CR patients for the first 15 patients (6)</td>
</tr>
</tbody>
</table>

IV indicates intravenous; SC, subcutaneous.
Response:

Decitabine response with chromosome 7 abnormality in MDS, and decitabine optimal schedule

The observation of Rüter et al regarding the favorable response of patients with myelodysplastic syndrome (MDS) and chromosome 7 abnormalities to decitabine is interesting. We had previously analyzed the prognostic factors associated with decitabine therapy in our patients with higher risk MDS. We did not find an association between pretreatment cytogenetic abnormalities and response, but found, by multivariate analysis, that the presence of chromosome 5 or 7 abnormalities was associated with poor survival. Since this study classified the cytogenetic abnormalities slightly differently and correlated cytogenetic studies with complete cytogenetic response, we reanalyzed the data as reported by Ruter et al. This is summarized in Table 1. We could not confirm the positive effect of the presence of chromosome 7 abnormality with cytogenetic response on decitabine therapy. This may be due to differences in the study groups, the decitabine dose schedules, or the small number of patients involved in each of the 2 analyses.

We agree with Dr Giagounidis’ comments. The Bayesian randomization design allows for studies with smaller numbers of patients, but can be associated with higher rates of false-positive and false-negative results, depending on the operating characteristics of the design. In our study, we can firmly conclude that the decitabine 10-day intravenous schedule is unlikely to be more active, is definitely more cumbersome, and is likely associated with more toxicities. However, as stated in our discussion, the decitabine 5-day subcutaneous schedule may still be as effective as the decitabine 5-day intravenous schedule, and would offer an alternative delivery route. The concluding statement of Dr Giagounidis’ letter sums it up well: a comparison of the decitabine (100 mg/m² per course) 5-day intravenous versus 5-day subcutaneous schedule is needed but will require a larger comparative trial.

Table 1. Responses by IWG criteria

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>No. treated</th>
<th>No. (%) hematologic responses</th>
<th>No. (%) cytogenetic responses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CR Overall</td>
<td>Complete Partial</td>
</tr>
<tr>
<td>Chromosome 7 abnormality only</td>
<td>3</td>
<td>0 (0)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>Chromosome 7 abnormality + 1 other</td>
<td>8</td>
<td>1 (13)</td>
<td>5 (63)</td>
</tr>
<tr>
<td>Chromosome 7 abnormality + 2 others</td>
<td>20</td>
<td>7 (35)</td>
<td>15 (75)</td>
</tr>
<tr>
<td>Other abnormalities</td>
<td>38</td>
<td>13 (34)</td>
<td>28 (74)</td>
</tr>
<tr>
<td>Diphloid</td>
<td>46</td>
<td>19 (41)</td>
<td>31 (67)</td>
</tr>
</tbody>
</table>

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References

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