Erlotinib is a small-molecule tyrosine kinase inhibitor (TKI) of human erythroblastic leukemia viral oncogene homolog 1 (ErbB1)/EGFR that is approved for the treatment of NSCLC and pancreatic cancer. Although erlotinib has not been studied in AML, gefitinib, another EGFR-TKI, can induce neutrophil differentiation in several EGFR-AML cell lines. In this patient’s bone marrow biopsy, EGFR was expressed on stromal cells, including fibroblasts, but was undetectable on myeloblasts (Figure 1E). Erlotinib was well tolerated; complete remission was achieved within a month, and was durable for at least 6 months. In conclusion, this is the first report of a patient with AML who achieved complete remission following erlotinib. EGFR inhibitors may induce neutrophilic differentiation of AML blasts via effects on tyrosine kinases (or other targets) distinct from EGFR. Clinical trials of erlotinib in the treatment of AML are warranted.

Geoffrey Chan and Monika Pilichowska

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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References


To the editor:

Preferential cytogenetic response to continuous intravenous low-dose decitabine (DAC) administration in myelodysplastic syndrome with monosomy 7

We read with great interest the recent publication by Kantarjian and colleagues addressing the value of different outpatient low-dose decitabine (DAC) schedules in higher-risk myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia.1 By the Bayesian design of that study, the number of patients randomized to 2 of the arms that were considered inferior (based on a somewhat lower hematologic response rate) was quite limited. Cytogenetic responses were also reported,
however, not according to the 3 different schedules. Thus, it is unclear whether patients treated with the 5-day, 20-mg/m², intravenous 1-hour infusional schedule (considered by the authors to yield superior results) also showed a superior cytogenetic response rate compared with the 2 other schedules.

Their overall cytogenetic response rate of 33% (responses in different cytogenetic subgroups are not given) is well in line with previous results of several multicenter European trials of low-dose DAC (total dose of 120 to 225 mg/m² per course administered mostly as intravenous 4-hour infusional schedule over 72 hours every 6 weeks). In these studies we observed a cytogenetic response rate of 31% in the 61 patients with informative cytogenetic abnormalities. Interestingly, response rates differed among the cytogenetic subgroups: in patients with good-risk abnormalities according to the International Prognostic Scoring System, a 60% response rate was seen; with intermediate abnormalities, 20% responses; and patients with high-risk cytogenetics (ie, any chromosome 7 aberrations and/or complex abnormalities) had a 38% cytogenetic response rate.

Because for the other azanucleoside that is very active in MDS (ie, Vidaza [5-azacytidine]; Pharmion, Boulder, CO) particular efficacy has been suggested in MDS with sole chromosome 7 abnormalities, we have now expanded our previous analyses to address this possible “class effect” of azanucleosides. Reanalyzing our data according to the presence or absence of chromosome 7 abnormalities among these 61 patients, we arrived at the following results: in the 6 patients with isolated chromosome 7 abnormality, 4 achieved complete (n = 3) or major (n = 1) cytogenetic responses (67% total response rate). Median response duration in the 15 patients with complex abnormalities was 10.5 months, and this difference was statistically significant by Student t test. Median time to (cytogenetic) relapse was 13.5 months (range, 9 to 15 months). Median cytogenetic response duration in the 15 patients with other cytogenetic abnormalities was 8 months (range, 3 to 12 months), and this difference was statistically significant by Student t test.
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.

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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%.3 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

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<th>Table 1. Decitabine dosage and response rates in patient subgroups</th>
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<tr>
<td><strong>5-day IV dose</strong></td>
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<td>No. of patients</td>
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<td>No. of patients in CR (%)</td>
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(Estimated) CR patients for the first 15 patients (6) 3 4
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