To the editor:

Cyclosporine modulation in poor-risk acute myeloid leukemia

The recent report from the Southwest Oncology Group by List et al1 regarding the benefit of cyclosporine modulation of P-glycoprotein drug resistance in poor-risk acute myeloid leukemia (AML) was read with anticipation, as optimal regimens for this difficult patient population have remained elusive. Upon reviewing the paper, however, several concerns became apparent.

The use of one-sided analysis to determine superiority of the cyclosporine arm was explained as follows: “the principal objective of the study was to assess whether [cyclosporine A] improves treatment outcomes.” 1(p3214) But the paper acknowledges that the pilot study of cyclosporine modulation showed that “treatment with CsA delayed the hepatic elimination of bilirubin . . . resulting in reversible conjugated hyperbilirubinemia and increased systemic anthracycline exposure”1(p3212); therefore it seems difficult to justify dismissing the possibility that the cyclosporine arm could do worse than the control arm necessitating 2-sided analysis. This significant flaw in design diminishes the power of the study. This seems particularly important given that the primary end point of the study, increased complete remission (CR) rate with cyclosporine induction, was not reached and that the conclusions reached by the authors are based entirely on secondary and subgroup analysis.

The most powerful conclusion from the study is that cyclosporine modulation results in a significant improvement in the duration of remission and in overall survival. But the use of stem cell transplantation for patients in remission is a potent confounding variable for each of these results. The authors accurately point out that, among patients under age 60 who achieved CR, 9 of 25 (36%) of patients in the control arm and 17 of 39 (43%) of patients in the cyclosporine arm received stem cell transplantation. Comparison of the percentages of eligible patients transplanted in each arm appears tantalizingly similar. But an equally accurate manner in which to present this data is that, in absolute numbers, 8 more patients in the cyclosporine arm received transplantation. Although this number is small, this represents nearly 7% of the patients randomized to the cyclosporine arm and is nearly double the number of patients transplanted in the control arm. This small number is pertinent given that the basis of the significance favoring the cyclosporine arm at 2 years for relapse-free survival (RFS) in patients in CR and overall survival for all patients is, in absolute terms, 8 patients and 9 patients, respectively. Whereas the authors provide some statistical reasoning to support their conclusion that “the CsA effect was not attributable to transplantation in remission,” 1(p3215) this significant conclusion warrants more detailed analysis. Who were the patients that received transplants, and by what criteria was transplantation determined? What type of transplants did they receive? Was HLA matching similar between these groups? Was there transplantation-associated mortality? When dealing with such a small number of patients, a factor as random as the availability of matched siblings may dramatically affect the results.

Combining the improper use of one-sided analysis and the confounding effect of stem cell transplantation for patients in remission with a small but real imbalance in pretreatment cytogenetics favoring the cyclosporine arm, a clear conclusion that cyclosporine modulation has significant long-term benefit does not seem capable of eliminating type I error (ie, the probability of incorrectly concluding that there is a statistical difference in a data set). Although this study clearly shows that cyclosporine modulation in poor-risk AML results in a significant decrease in residual disease following induction therapy, the long-term significance regarding relapse-free survival and overall survival appears to be a matter of speculation.

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References


Response:

Benefit of cyclosporine modulation of drug resistance in patients with poor-risk acute myeloid leukemia

We thank Drs Beattie and Petruska for their comments and questions concerning our manuscript that raise important points relevant to all trials in patients with high-risk leukemia.1 The letter raises 2 issues regarding the design and analysis of the study. The first concerns the study’s underlying hypothesis, that the addition of cyclosporin A (CsA) to a regimen of daunorubicin (DNR) and high-dose cytarabine would improve treatment outcomes. The prior experience with CsA provided adequate justification for optimism that adding CsA would have a net benefit. In the phase I/II trial performed in patients with poor-risk AML, coadministration of CsA and infusional daunorubicin yielded a high rate of complete remission and consistently eliminated MDR1-overexpressing clones in sequentially analyzed relapse specimens.2 More importantly, dose-limiting toxicity was not encountered, despite the fact that CsA delayed the hepatic elimination of bilirubin and daunorubicin. Generally, one-sided design and analysis are appropriate for phase III studies that investigate the effect of adding an agent to a standard regimen, since the ultimate clinical recommendation is inherently one-sided: if there is evidence that adding the agent is beneficial, then its use may be recommended. Otherwise, the agent should not be added, and whether it has no effect or is detrimental is immaterial to this recommendation.
The possibility that the CsA arm might “do worse” was not, as the letter alleges, “dismiss[ed]” by the design or analysis of the study. The stated principal objectives of the trial included comparison not only of induction response and survival but also of the toxicity of the 2 regimens. In addition, the study’s protocol required that the planned interim analyses include assessments of whether the study should be terminated early due to evidence against a clinically meaningful benefit from CsA, a much easier condition to satisfy than evidence of worse outcomes with CsA, which a 2-sided design would have required.

The assertion in the letter that designing the study to achieve an inherently one-sided objective “diminishes the power of the study” is rather misleading. For any given one-sided alternative hypothesis, that is, for any given magnitude of CsA benefit, a one-sided comparison has greater statistical power than the corresponding 2-sided comparison based on the same sample size and critical level. Therefore, employing a 2-sided test when a one-sided test is appropriate in fact “diminishes” statistical power. In other words (and we assume this is the authors’ intended point), a 2-sided design requires a larger sample size than a one-sided design in order to have equivalent statistical power to detect any given magnitude of CsA benefit. This is indeed true but is simply a consequence of the fact that the objective of the study determines its design (including sample size). Requiring a 2-sided study’s sample size when a one-sided design is appropriate prolongs the duration of the study and delays the availability of clinically important information.

The second issue raised in the letter concerns the role of stem cell transplantation. The analysis reported in the paper1(p3215) was performed to investigate a specific question: whether the apparently beneficial effects of CsA might be attributable to an increased likelihood of receiving stem cell transplantation in remission. The letter requests “more detailed analysis” of the characteristics of the transplants and patients who received them. It is ironic that the authors criticize the use of “secondary and subgroup analysis” in one paragraph and then call for a much more extreme form of such analysis in the following paragraph. Any attempt to attribute differences in outcomes to differences in events following randomization, which is of course not based on protocol-directed “intent-to-treat” comparisons, is subject to unquantifiable biases. Our analysis of the impact of transplantation is certainly subject to this criticism, and we were therefore careful to claim only that the results “suggest[ed] that the CsA effect was not attributable to transplantation in remission.”1(p3215)

The requested “more detailed analysis” is an attempt to identify these biases but is doomed to inconclusiveness. The decision as to whether or not a patient receives a transplant of a given type is the result of a complex balance of the expectations, experiences, resources, and preferences of the physicians, the patient, and even the patient’s family and friends. The decision process is highly individualized, quite possibly differing according to prognosis and/or between treatment arms, and is largely undocumented. Therefore the question, which addresses a non-protocol-directed decision (ie, “Who were the patients that received transplants and by what criteria was transplantation determined?”), cannot be answered with sufficient detail and confidence to ensure that the possibly large biases are all accounted for.

In addition, the authors make a strong argument against the very analysis they request, by emphasizing that “[w]hen dealing with such a small number of patients, . . . [small, uncontrolled effects] . . . may dramatically affect the results.” This is certainly true of any attempt to try to identify biases arising from the decision processes that led to transplantations in only 26 patients.

Finally, we note that the letter incorrectly implies that complete remission (CR) rate was the sole primary end point of the study. In fact, as described above, overall survival and toxicity were also primary end points of the study.

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References

To the editor:

Binding of imatinib by α1-acid glycoprotein

In their recent report Jørgensen et al1 raised doubts on the ability of α1-acid glycoprotein (AGP) to bind and inhibit imatinib (STI571), as shown in our previous report.2 We would like to comment on this paper, on some methodological inaccuracies of their paper, and on additional in vivo data that in our opinion strongly indicate an important role for AGP in modulating imatinib bioavailability and pharmacokinetics (PK).

First, it is well known that chromatographically isolated AGP, the one used by Jørgensen et al, show less-efficient binding of drugs in general than chemically isolated AGP, the one used in our paper.3 It is surprising in this respect that Jørgensen et al never used as a control our preparation of AGP.

Second, in their paper the authors state that our AGP preparation, supplied by Sigma, “risks desialylation of the protein.”1(p714) But the authors fail to acknowledge that such a phenomenon has been associated with a decrease (or with no change at all) in drug binding,1,5 and not with an increase in binding, as their data apparently suggest.

Third, the drug-binding assay shown is misleading. Quenching of AGP fluorescence requires detailed information on a given drug’s binding site to AGP, since several binding sites for drugs on AGP are known; this information was not provided for imatinib. In addition, quenching should be shown using progressively increasing concentrations of the drugs being studied and not, as done by Jørgensen et al, by comparing 2 different drugs, used at a single concentration, which differed in the 2 drugs studied (imatinib at 1 μM, chlorpromazine at 2.5 μM).

Fourth, in vitro experiments using unmanipulated AGP (in the form of sera containing different concentrations of AGP) performed by 2

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