Response:

Discrete stem cell subsets

It is delightful that our paper, “The hematopoietic stem cell compartment consists of a limited number of discrete subsets,” has sparked the interest of colleagues in the modeling field. To recapitulate, we showed the following: (1) Only a small fraction of all possible behaviors was realized by hematopoietic stem cells (HSCs) in vivo. (2) Based on the kinetics of repopulation, HSCs could be classified into groups. (3) HSCs in different groups differed in self-renewal capacity. (4) HSCs in different groups can differ in cell-surface phenotype. (Additional data were presented recently.)

Kirkland, Roeder and Loeffler, Quesenberry et al, and Quesenberry have each developed models that describe the HSC compartment as a continuum of functions. We agree that many paradigms in HSC biology should be revisited to incorporate recent developments, particularly in the area of molecular control of HSC behavior. Models are powerful tools to complement and integrate experimental data, if they make testable predictions that allow their validation. It has been argued that a useful model should be a hypothesis generator. It is a bit challenging for nonaficionados to discern the predictions made by the continuum models. Thus, the letter by Kirkland et al opens a welcome dialogue.

In their letter, Kirkland et al question whether our data support or challenge their models. Let us dispense with the discussion of some of the finer points of the different flavors of the continuum models and focus on the central point. The central argument of these models appears to be that behavior of HSCs should be reversible, creating an ephemeral heterogeneity of HSC functions. Such an extreme flexibility (reversibility) would predict that a single HSC could recreate all, or at least a good part, of the functional heterogeneity seen in the HSC compartment. However, we showed that each individual HSC generates daughter HSCs that are very similar to each other in their differentiation and proliferation behavior. Notably, single HSCs did not recreate the heterogeneity seen in the original HSC compartment. These data support the view that HSC differentiation and proliferation capacities are epigenetically fixed on the level of individual HSCs. In other words, HSC heterogeneity is permanent at least in the adult mouse.

On face value, it is difficult to integrate these data with the notion that HSC behavior is reversible. However, experience from quantum mechanics has shown that both discrete and continuum approaches are needed to fully explain the behavior of subatomic particles. Whether HSCs do in fact behave like quanta awaits experimental resolution.

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References


To the editor:

Increased mortality with FLA compared with ADE chemotherapy in high-risk AML

In the MRC AML-HR trial, Milligan et al describe inferior overall survival with fludarabine and high-dose cytosine (FLA) compared with conventional cytosine, daunorubicin, and etoposide (ADE) reinduction chemotherapy for high-risk acute myeloid leukemia (AML). As type I error is a potential explanation of these results, further information to clarify the mechanism underlying the reduced overall survival with FLA would be helpful before a potentially useful regimen is abandoned.

The difference in overall survival appears attributable to increased death in remission (34% vs 12%; P = .1) in the FLA compared with ADE group. Although not statistically significant, the trial was not powered to explore this parameter, and other adverse predictors (resistant disease, induction death, and relapse rate) were almost identical. An analysis of deaths in remission comparing the 2 treatment arms may clarify the inferior overall survival with FLA. For example, fludarabine predisposes to opportunistic infections, may influence choice of subsequent consolidation therapy, and may also lead to an increased risk of second malignancy. No information on the use of prophylactic antimicrobials was given.

The MRC AML-HR trial has made an important contribution to our understanding of the optimal therapeutic approach in high-risk AML. Further information would be valuable to continue development or modification of current treatment algorithms in this challenging disease.

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Increased mortality with FLA compared with ADE

We agree with Lane et al that the difference in overall survival between fludarabine and high-dose cytosine (FLA) and cytosine, daunorubicin, and etoposide (ADE) could be a chance effect. The hazard ratio, as reported in our paper, has a 95% confidence interval (CI) that ranges from 1.01 to 1.77. Thus, our result is compatible with there being no adverse impact of FLA on survival; on the other hand, it is also compatible with a 75% increase in mortality. Because of this uncertainty, we were cautious in our interpretation: in the abstract we concluded that “FLA may be inferior,” whereas in the discussion we said that “we found no evidence that fludarabine with high-dose cytosine was a better treatment than the standard MRC schedule of ADE.” We believe that the latter statement is justified since, based on our results, it seems unlikely that FLA is actually better than ADE.

With regard to deaths in complete remission (CR), the Kaplan-Meier estimates at 4 years are a bit misleading and make it appear as if the death rate is nearly 3 times greater in the FLA arm (34% versus 12%). This is because there was a small number of late events in the FLA arm (4 deaths beyond 1 year—with only a small number of patients at risk, each event adds 3%-4% to the Kaplan-Meier estimate), but none beyond 1 year in the ADE arm. In terms of crude death rate, 20% (17/83) of patients in the FLA arm died in CR compared with 12% (10/84) in the ADE arm. There is no clear explanation for this moderate, and nonsignificant, difference. More patients died following transplantation in the FLA arm than in the ADE arm (10 versus 5, with 36 versus 37 transplantations performed, respectively), though this difference is not significant ($P = .13$). Of the remaining 12 deaths in CR, the majority was from infection as would be expected, but there was no excess with fludarabine (4 in each arm). None of the deaths in CR were related to second malignancy. Although there was no difference between the arms in relapses (83 FLA, 84 ADE), slightly more of the relapsing FLA patients have subsequently died (45 FLA, 39 ADE). Thus, a number of factors combine—3 more deaths without CR, 7 more in CR, 6 more after relapse—to give the cumulative excess of 14 deaths in the FLA arm, and the borderline significant adverse effect of FLA on survival compared with ADE, as reported in our paper.

Although we have not identified any clear reason for the apparent adverse impact of FLA on survival, and on the basis of the CI in our study (lower limit of hazard ratio CI = 1.01), it may not actually be any worse than ADE; it could, however, be a lot worse (upper limit of CI = 1.77), so it would be reasonable on the current evidence to avoid using FLA routinely.

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Reference

To the editor:

Osteonecrosis of the jaws in newly diagnosed multiple myeloma patients treated with zoledronic acid and thalidomide-dexamethasone

In recent years, an increasing number of reports have pointed out the association between osteonecrosis of the jaws (ONJ) and the use of bisphosphonates as therapy of neoplastic bone disease or benign osteoporosis. The pathogenesis of this complication is unknown, although bisphosphonate-induced impaired bone resorption is likely to play a crucial role. Moreover, the relative contribution of microtrauma from chewing, repeated dental procedures, poor oral hygiene, cancer bone involvement, and concomitant chemotherapy has not been clarified yet.

In an attempt to identify the incidence of ONJ in a large, homogeneous series of patients with newly diagnosed multiple myeloma (MM) and to define the possible pathogenetic role of concurrent antmyeloma therapy, we retrospectively reviewed a series of 259 consecutive patients with symptomatic MM who were enrolled in the Bologna 2002 clinical trial. By study design, all patients received 4 months of primary therapy with thalidomide (200 mg/d) combined with high-dose dexamethasone (40 mg/d on days 1-4, 9-12, and 17-20 or on odd cycles and on days 1-4 on even cycles) followed by double autologous transplantation with 200 mg melphalan/m2. Daily thalidomide (200 mg/d) and monthly courses of dexamethasone were continued until the second autologous transplantation. Intravenous zoledronic acid 4 mg every 28 days was administered throughout the whole treatment period and continued thereafter, at physician’s discretion. Only patients receiving zoledronic acid for longer than 4 months were included in the present analysis.

Overall, 9 patients (3.47%) presented with suspicious findings of ONJ, which was subsequently confirmed at oral/maxillofacial diagnostic workup. As previously reported, the duration of exposure to bisphosphonates was closely related to an increased

References
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