Response:

Neither age nor mobilization likely to have effect

Dr Mehta raises 2 important points. The first relates to the ages of the patients who received DLI in our study by escalating dose regimen (ESC) or bulk dose regimen (BDR) respectively. There was no significant difference between the 2 groups [BDR n = 28, mean age 40.8 (19.5 to 57.6), EDR n = 20, mean age 36.9 (23.9 to 52.8), P = .13]. The slightly higher age in the BDR group can be accounted for by the fact that the ratio of sibling recipients to unrelated donor recipients was higher in the BDR than in the EDR group. Since patient age is indeed a major factor predictive of incidence of GVHD.

The second point regards the use of G-CSF mobilized lymphocytes. None of our patients received mobilized peripheral blood mononuclear cells; so the low incidence of GVHD in the EDR group cannot be attributed to the use of this technique. We would like to make some comments to this point. First, the possibility that G-CSF mobilized PBMC may reduce the incidence of pancytopenia remains to be demonstrated. In fact, a preliminary report from the Seattle transplant group showed that the administration of G-CSF mobilized lymphocytes does not prevent the DLI-induced aplasia. Nevertheless, pancytopenia was not a major problem in our cohort of patients; when it did occur, it resolved spontaneously or after the infusion of the donor stem cells. The second aspect regards the effect of G-CSF on donor lymphocytes. Although the suggestions provided by Dr Metha may be of value, there is no clear evidence that G-CSF can commit the donor T cells toward a leukemia-specific immune response. The ability of G-CSF to potentiate the immune effectors also remains controversial.

In summary, we feel that the approach we have been using to administer DLI on an escalating dose regimen is effective and is associated with little toxicity, and thus we do not consider any change to be justified.

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References


To the editor:

Benzene and multiple myeloma: appraisal of the scientific evidence

The recent paper by Bergsagel et al raised questions of scope, content, and provenance. Goldstein and Shalat have addressed many of the issues of scope and content in their review, and a response to their letter has been received from the authors of the paper. We will not address those issues again. However, the issue of the article’s provenance has not been addressed, and it is to that provenance we now turn.

When the Bergsagel review was published, one of us wrote to the editor to ask what the source of funding for this paper might have been. The editor responded at that time that since Blood did not have a policy that required financial disclosure, he had no information on the source or sources of funding for the paper. He recommended that we write the authors to obtain this information. Two letters to the authors went unanswered. Further inquiry to the editor provided welcome assurance that Blood’s editorial policy had been changed [New policy follows the response to this letter—Ed]. Blood will require financial disclosure in the future. However, the policy could not fairly be applied retroactively. Because the provenance of the Bergsagel paper remained at issue, the editor invited a letter to encourage the authors to provide the financial support information.

In the interim, we have learned that the Bergsagel paper was prepared in support of litigation in which the causality of multiple myeloma by benzene was at issue. Two of the authors have published a series of papers for this purpose over the past years.

One is an employee of a major petrochemical company, and the other an epidemiologist whose work on behalf of the petrochemical industries is well known. In a sworn deposition in the litigation at issue, Professor Bergsagel testified as follows:

Q. What precipitated Dr Wong contacting you to co-author an article, if you know?
R. Yes I do know. We were both retained as expert witnesses by James Galbraith of Galveston, Texas in a litigation case of Donald Ballard versus Amoco. That case never came to trial. But Mr Galbraith wanted us to collaborate with three other hematologists and create a consensus statement, and so we began the article as a consensus statement for that case.
Q. Did Mr Galbraith ask you to publish your consensus statement?
R. Well the case was settled before we got the consensus statement published. And I asked him if he would mind if we were to develop this statement into an article that could be published in a hematology journal, and he encouraged me to do that.
Q. And Mr Galbraith represented?
R. He represented Amoco.
Q. A petroleum company?
R. That’s correct.
Clearly, the current paper was litigation-driven. While this provenance does not in and of itself invalidate the authors’ findings, which will stand or fall on their internal consistency and conclusions, it does raise questions of fairness, which should be addressed by the authors themselves. Scientific testimony in court is offered on behalf of one side or another, and it does not represent consensus, but rather the opinion of the expert or experts involved. That opinion testimony is subject to the trial treatments of cross-examination. However, the publication of a review article in a journal does not undergo such cross-examination. Without vigorous debate, subsequent letters and responses, and the editor’s good will and desire for fairness, as in this instance, such a litigation-support document that was prepared to further a particular point of view, published in a respected peer-reviewed journal like Blood, might improperly enter the literature as authoritative. Salting the literature in this fashion does not help to further scientific knowledge.

We applaud the willingness of Bergsagel et al to enter into the courtroom debate on the hematopoietic consequences of benzene exposure. We hope that, if they continue to participate in this process and continue to write about it, they will make their editors, reviewers, and readers aware of the provenance of their work.

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Response:

Benzene exposure and multiple myeloma

Teitelbaum et al question the provenance of our recent review article on benzene exposure and multiple myeloma.1 Since their comments were addressed primarily to 2 of the authors, the undersigned have consulted the others, and they have agreed that it would be appropriate for us to respond.

Teitelbaum et al are correct in stating that we were retained as experts in a legal case involving benzene exposure and multiple myeloma (Fannin vs Norfolk & Western Railway Co). However, we have been engaged in research on multiple myeloma and benzene and have published on the subject long before our involvement in the Fannin case. Furthermore, what Teitelbaum et al do not reveal in their letter is the fact that they are very active in working with attorneys in litigation themselves. Similarly, both Goldstein and Shalat work with attorneys in litigation matters as well.

As to the provenance of the review article, although individually we have previously published articles on different aspects (clinical vs epidemiological) of benzene and multiple myeloma, we felt there was a need for a more comprehensive review paper on the subject. Many new scientific investigations (particularly epidemiological studies) on benzene and multiple myeloma have been published during the last 2 decades, but the results have not been summarized in any review. This lack of an up-to-date review was clear to us while we were reviewing the literature 4 or 5 years ago. In spite of the recent studies, some “experts” still base their opinions solely on outdated case reports. Mr Galbraith (an attorney) suggested that we might consider writing a comprehensive review. We agreed that such a review was needed. To ensure the scientific quality of our review, we enlisted several other scientists in hematology, oncology, and epidemiology as coauthors. Our review represented a consensus of all the authors of the article. Furthermore, the article was also subjected to the rigorous peer-review process required by Blood. The review was based on our own research over the years as well as our assessment of the pertinent literature over the last 2 decades. The preparation of the review was not funded by any party. Even the cost of the reprints was paid by us personally.

In our review1 and our response to Goldstein and Shalat,2 our assessment of the relationship between benzene exposure and multiple myeloma was based on scientific data (in particular, recent epidemiological studies). Neither Goldstein and Shalat3 nor Teitelbaum et al have offered any scientific data to counter our argument. In particular, they have not offered even one epidemiological study that demonstrates a causal relationship between benzene exposure and multiple myeloma. Causation assessment of chronic diseases such as multiple myeloma, whether in the medical or legal context, should be based on scientific data. Likewise, expert opinions should be based on the most up-to-date scientific data as well.

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References

References


To the editor:

DAP-kinase CpG island methylation in acute myeloid leukemia: methodology versus biology?

Acute myeloid leukemia (AML) is a clonal disorder evolving from myeloid progenitor cells on the background of a number of genetic changes including balanced translocations1,2 and alterations of tumor suppressor genes and proto-oncogenes.3 Recently, transcriptional silencing of tumor suppressor genes by hypermethylation of promoter CpG islands has emerged as an event that may contribute to the leukemic phenotype. Among the genes found to be hypermethylated at significant rates in AML are p15INK4B,4-6 the estrogen receptor,7 and HIC1.8 By this letter we would like to draw attention to methodological features that may cause confusion in the interpretation of data on promoter methylation.

In a recent issue of Blood, Katzenellenbogen et al9 reported that hypermethylation of the death-associated protein kinase (DAP-kinase) is a common alteration in B-cell malignancies. DAP-kinase is a 160-kd cytoskeleton-associated protein with serine/threonine kinase activity. It functions as a positive mediator of interferon-γ induced cell death10 and is furthermore involved in FAS and TNF-α induced apoptosis.11 Using a methylation-specific polymerase chain reaction (MSP) assay12 Katzenellenbogen et al found that 100% (9 of 9) of samples from Burkitt’s lymphoma and 84% (21 of 25) from other B-cell lymphoma patients were methylated in the DAP-kinase 5’ CpG island. In contrast, no methylation was found in T-cell lymphoma or T-cell acute lymphoblastic leukemia samples. In AML, 3.8% (1 of 26) of pediatric samples and 33% (2 of 6) of adult samples were found to contain methylated DAP-kinase alleles.

We recently developed a novel method, “bisulfite-DGGE,” that detects aberrant methylation and provides a detailed display of the composite pattern of clonotypic epigenotypes within a sample of DNA.6 This method combines bisulfite treatment of genomic DNA with nondiscriminatory PCR amplification of methylated and unmethylated sequences, followed by resolution of alleles with varying methylation density by denaturing gradient gel electrophoresis (DGGE). By using this method, we demonstrated a highly heterogeneous pattern of p15INK4B methylation in AML samples.

Prompted by the above mentioned report,9 we analyzed leukemic blasts from AML patients and leukemic cell lines for methylation in the DAP-kinase CpG island using both MSP and bisulfite-DGGE. MSP was performed with primers identical to those described by Katzenellenbogen et al,9 while for bisulfite-DGGE, we designed a pair of primers to amplify a 103-bp region of the DAP-kinase CpG island. In contrast, no methylation was found in T-cell lymphoma or T-cell acute lymphoblastic leukemia samples. In AML, 3.8% (1 of 26) of pediatric samples and 33% (2 of 6) of adult samples were found to contain methylated DAP-kinase alleles.

In concordance with the previous report,9 we found, by both MSP and bisulfite-DGGE analysis, that the Raji cell line is completely methylated in the DAP-kinase CpG island, and that the HL-60 cell line is partially methylated (Figure). MSP analysis of clinical AML samples revealed methylated alleles of the DAP-kinase in 42% (19 of 45) of de novo adult AML cases and in none of four de novo pediatric AML cases (Figure). Direct sequence analysis of the PCR products showed that all cytosines at CpG sites had remained as cytosine during bisulfite treatment and all samples were extensively methylated in the p15INK4B CpG island with only a small fraction of unmethylated alleles present.

Note: Prior to receiving Teitelbaum et al’s letter and Bergsagel et al’s response, the Editorial Board of Blood initiated a new policy requiring disclosure of any significant financial interests in subjects covered in the text of published papers in the Journal. This policy is stated in the Author Guide of this and other issues of Blood. However, this disclosure policy was not in place at the time of writing of the review “Benzene and multiple myeloma,” which has prompted the above exchange of letters.—Editor
Benzene and multiple myeloma: appraisal of the scientific evidence

Daniel Thau Teitelbaum, Nachman Brautbar, Myron Mehlman and Joseph LaDou