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Therapy-related myeloid leukemia: stochastic or idiosyncratic?

Richard A. Larson

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● ● ● NEOPLASIA

Comment on Coriu et al, page 829

Constipated myeloma

P. Leif Bergsagel WEILL CORNELL MEDICAL COLLEGE

The molecular basis of nonsecretory myeloma in one patient is shown to be due to a crippling frameshift mutation in the kappa constant region.

Most patients (~ 80%) with multiple myeloma have a monoclonal immunoglobulin (Ig) detectable in the serum, usually IgG or IgA. About 18% have only monoclonal light chains detectable in the urine (light-chain multiple myelomas [LCMMs]). Finally, about 2% do not secrete any immunoglobulin (nonsecretory multiple myelomas [NSMMs]). Recent analyses of LCMMs have shown that the tumors lack a functional IgH rearrangement, providing a molecular basis for this condition.¹ There has not been a comprehensive analysis of NSMMs, and previous reports have emphasized acquired mutations in the immunoglobulin light chain variable genes that lead to a block in secretion.²⁻⁴ Thus from the information available there appears to be a fundamental difference in these 2 conditions, which otherwise share many features (eg, very high incidence of t(11;14)). On the one hand, LCMM lacks a functional IgH DNA rearrangement, and hence there is no RNA or protein. On the other hand, NSMM has an IgL DNA rearrangement, RNA, and protein, but suffers from crippling mutations.

In this issue, the molecular basis of nonsecretory myeloma in one patient is shown to be due to a crippling frameshift mutation in the κ

constant region. Coriu and colleagues show that a 2-base deletion in codon 187 resulted in the loss of the normal stop codon. There was a loss of 2 cysteine molecules that are necessary for intrachain and interchain disulfide bonds. The authors postulate that the absence of C194 disrupted the 3-dimensional features of the molecule and prevented binding with the cysteine in the first heavy-chain C-domain. The misfolded κ chains were retained within

the plasma cell. They show that this results in an abnormal-sized protein that reacts with some but not all anti- κ antibodies. In contrast to previously described mutations of the variable region, this represents a novel mechanism for nonsecretory myeloma. ■

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● ● ● NEOPLASIA

Comment on Offman et al, page 822

Therapy-related myeloid leukemia: stochastic or idiosyncratic?

Richard A. Larson UNIVERSITY OF CHICAGO

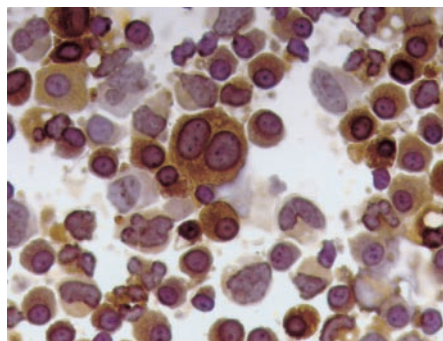
Just as life begins to return to normal, some solid organ transplant patients develop leukemia. Why?

Patients who have received cytotoxic therapy with chemotherapy drugs and/or radiotherapy are at risk for long-term complications from their treatment, including therapy-related myelodysplastic syndrome (tMDS) and acute myeloid leukemia (tAML). Although a causal link has not yet been proven, these neoplasms are thought to be a direct consequence of mutational events caused by cytotoxic therapy and to be independent of the primary disease. Careful clinicopathologic and cytogenetic analyses of individual cases by many investigators have defined distinctive subtypes of this disease.¹

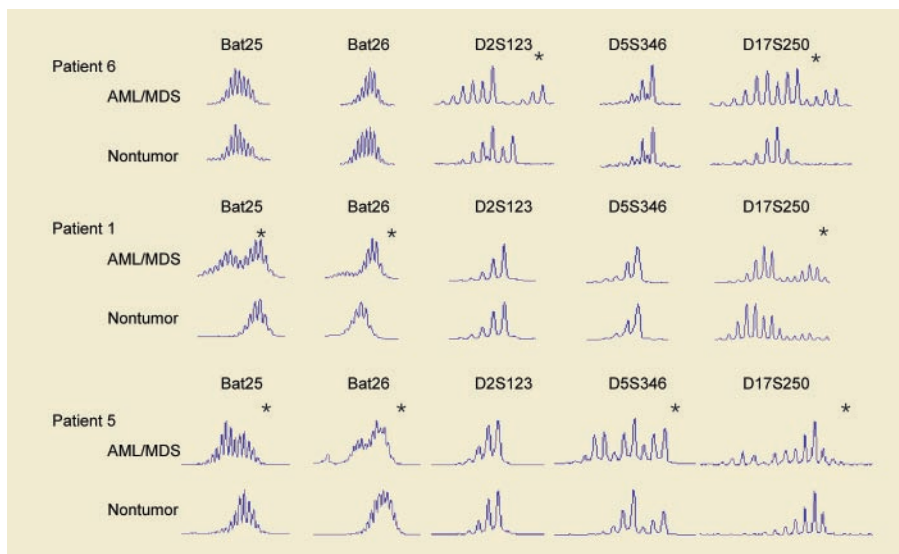
Large epidemiologic surveys have defined high-risk patient populations. Patients with Hodgkin lymphoma were the first large cohort of cancer patients who experienced prolonged survival; hundreds of cases of therapy-related leukemia have now been reported within this group. More recently, treatment has extended

the survival of patients with other cancers and they too have become at risk. In a recent report on 306 patients with therapy-related myeloid leukemia studied at the University of Chicago, 171 had lymphoma or myeloma as their primary disease, and 117 had solid tumors.² Of note, 18 had received cytotoxic therapy for nonmalignant disorders, such as autoimmune diseases, or for immunosuppression after renal allografts.

Both ionizing radiation and many, but not all, chemotherapy drugs alter cellular DNA. If not repaired, this damage is most often lethal to cells. This, of course, is the desired consequence if the target cell were a tumor cell. Occasionally, however, nonlethal and heritable mutations occur in single somatic cells. Such an alteration in DNA might involve a single base change, deletion or inactivation of a growth suppressor gene, or changes in the expression of certain critical oncogenes or



Immunocytochemical analyses of plasma cells from the patient with NSM and chemical characterization of the nonsecreted κ light chains. See the complete figure in the article beginning on page 829.



Microsatellite instability in AML/MDS from recipients of organ transplants. See the complete figure in the article beginning on page 822.

growth factor receptor genes. Alkylating agents, in particular, and radiation both possess strong mutagenic activity in vitro plus carcinogenic potency in vivo.

It has not yet been possible to determine whether the development of tMDS/tAML is a stochastic event, occurring by chance, or whether certain individuals are at higher risk, perhaps due to a DNA-repair deficiency or a heritable predisposition, such as altered drug metabolism. The identification of such an underlying pre-existing condition would help the screening and counseling of patients at the time of treatment for their primary disease.

Offman and colleagues now add important new data that may illuminate one mechanism for the etiology of therapy-related leukemia. Analyzing data for 180 000 recipients of heart, lung, or kidney transplants from 300 transplant centers, the authors report a significantly increased risk for developing tMDS/tAML among these recipients. A latency of 3 to 4 years was observed, and the risk was proportional to the dose of the thiopurine azathioprine received. Additionally, they confirm that thiopurines select for mismatch repair (MMR)-deficient cells in culture. Finally, they report that all 7 tAML patients examined demonstrated microsatellite instability, diagnostic for defective MMR.

Lymphoproliferative disorders that occur within a few months after transplantation are most likely due to immunosuppression from agents such as cyclosporine. In contrast, the prolonged use of thiopurines after solid organ transplants may favor the

outgrowth of MMR-deficient cells, perhaps even within hematopoietic stem cells. Such a

● ● ● TRANSPLANTATION

Comment on de Lima et al, page 857, and de Lima et al, page 865

Fludarabine finds its significant other?

John Barrett NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Fludarabine-based conditioning regimens for allogeneic stem cell transplantation offer distinct advantages for reducing treatment-related mortality; the problem is how to conserve low toxicity while maintaining antileukemic efficacy.

When bone marrow transplantation conditioning regimens were first used to treat leukemia, the transplants were intended primarily as a means to reconstitute marrow function after a massive leukemia-ablative treatment with “supralethal” doses of total body irradiation (TBI). The 1990s brought a realization that the donor graft could strongly attack leukemia through an alloimmune graft-versus-leukemia (GVL) effect. Transplantation conditioning regimens for malignant diseases are, therefore, now designed not only to cytoreduce leukemia but also to establish donor immunity to provide a GVL effect. This new thinking stimulated the M.D. Anderson and other marrow transplantation teams to explore reduced-intensity conditioning regimens, focusing more on the establishment of a GVL effect and less on the cytoreductive power of the regimen. Fludarabine has be-

come a central component of these regimens because of its potent immunosuppressive but nonmyeloablative action. An immediate spin-off was the safer application of stem cell transplants to older and debilitated patients. However, these regimens often failed to control disease, and the search for safe antileukemic agents to combine with fludarabine has continued.

Two papers in this issue of *Blood* describe 3 fludarabine-based stem cell transplantation regimens studied at the M.D. Anderson Cancer Center. The first study from de Lima and colleagues compares outcomes of older patients receiving FAI (fludarabine, cytosine arabinoside, and idarubicin), a nonmyeloablative regimen, with FM (fludarabine and melphalan), a myeloablative regimen. Predictably, the FM patients had more treatment-related complications and higher treatment-related mortality

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