[News * Analysis * Commentary * Controversy]

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Counterfeit Drugs: IOM Probing How to Stop the Worldwide Danger

BY PEGGY EASTMAN

The discovery of a counterfeit version of Avastin in the U.S. market is only the latest example of the global problem of falsified and substandard pharmaceutical products. Here are the details of the just-announced study by the Institute of Medicine that will delve into the far-reaching implications and attempt to find solutions.

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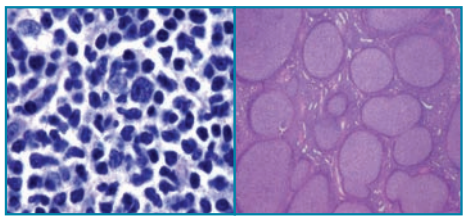

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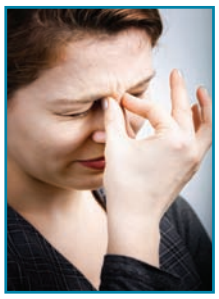

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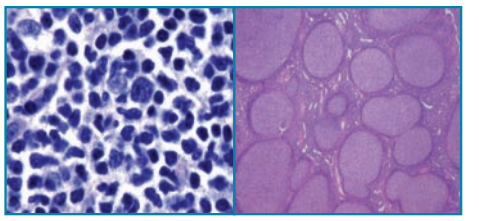
New Insights into Follicular Lymphoma from Sister-to-Sister Transplantation



BY MARK FUERST

SAN DIEGO—When a 41-year-old woman was diagnosed with chronic-phase chronic myeloid leukemia (CML), she received a bone marrow transplant and subsequent leukocyte infusion from her sister. These treatments controlled her leukemia, but more than seven years later both sisters developed follicular lymphoma, suggesting transfer of a common ancestor cell. This rare opportunity to study the disease may provide oncology researchers with new insights into lymphoma development.

"Follicular lymphoma has a very long latency of acquiring mutations. This unique setting allowed us to check the time course for each mutation," said Oliver Weigert, MD, a post-doctorate fellow in hematology/oncology at Dana-Farber Cancer Institute, who reported the findings at the American Society of Hematology Annual Meeting (*Abstract 3671*). "We were able to make an important discovery about the biology of the disease by looking very deeply at these two cases.

"It's a proof of principle that a rare disease can be studied in vivo. This means there is hope for rare diseases that don't have 100,000 cases."

The research was also published as a full study in *Cancer Discovery (2012;2:47-55)*.

Asked for his opinion for this article, Nathan Fowler, MD, Head of Low-grade Lymphoma and Assistant Professor of Medicine in the Department of Lymphoma/Myeloma at the University of Texas MD Anderson Cancer Center, who was not involved with the research, said, "As clinicians we know that the history of follicular lymphoma can be dramatically different in different patients. It remains difficult to predict why one patient lives two years and another one lives 20 years. The answer may lie in undiscovered mutations.

OLIVER WEIGERT, MD: "Follicular lymphoma has a very long latency of acquiring mutations. This unique setting allowed us to check the time course for each mutation. We were able to make an important discovery about the biology of the disease by looking very deeply at these two cases."

"Perhaps deep sequencing can find these hidden clues. This technology could lead to improved identification of rare genetic events which could have prognostic impact."

The concept of a donor passing a malignancy to a recipient is well documented and considered a minimal risk to those in the transplant community. But this case gave the researchers the opportunity to understand the genetic abnormalities that led to follicular lymphoma in both cases.

Study Details

In the study, which was funded by a Stand Up To Cancer Innovative Research Grant, Weigert and colleagues sequenced the DNA of samples derived from the two sisters as well as a frozen sample of the leukocyte infusion to determine the genetic lesions that led to the lymphoma. They found that both sisters had identical BCL2/IGH rearrangements and the same V(D)J rearrangement. The team also identified 15 mutations that were present in both lymphomas.

The researchers recovered 14 of these mutations from the donor lymphocyte infusions using ultra-deep sequencing—a finding that indicates that a lymphoma ancestor harboring these mutations was passed from the donor to the recipient seven years before clinical presentation.

"We were able to combine clinical activity with laboratory expertise to gain a real insight into the biology involved," said the study's senior author, David M. Weinstock, MD, Assistant Professor of Medicine at Dana-Farber. "The presence of an ancestor cell harboring many but not all mutations raises the possibility that the reason follicular lymphoma remains uncured is that the vast majority of cells are eradicated with chemotherapy but some pool of cells is not like the other follicular lymphoma cells. We may be able to identify the cells that carry some mutations and have inherent resistance to chemotherapy."

Follicular lymphoma is characterized by the translocation t(14;18), which results in overexpression of the anti-apoptotic protein BCL2 through juxtaposition to the immunoglobulin heavy chain (IGH) locus. Weigert noted that although additional genetic aberrations are required and recurrent mutations have been identified, the timing of development remains unknown.

"We performed ultra-sensitive mutation detection to define in vivo clonal diversification in paired follicular lymphomas from a donor-recipient sibling pair that presented several years after hematopoietic cell transplantation," he explained.

The sister who was the CML patient underwent myeloablative bone marrow transplantation from her HLA-matched sister in 2000. She received three donor leukocyte infusions (DLI) for molecular relapse, the last one in June 2002. In November 2009, the donor was diagnosed with grade 2/3A follicular lymphoma. Six months later, the recipient received the same diagnosis.

"The follicular lymphomas shared identical BCL2/IGH rearrangements, which was also recovered from the DLI at a frequency of 1-in-2000 cells," he said. Both follicular lymphomas also shared the same V(D)J rearrangement, with the exception of single base-pair mismatches and insertions/deletions consistent with ongoing somatic hypermutation during clonal divergence. There were also indications that the common ancestor had initiated somatic hypermutation.

> "This is proof of principle that a rare disease can be studied in vivo. This means there is hope for rare diseases that don't have 100,000 cases."

Sequencing of both follicular lymphomas identified 12 single nucleotide variants (SNVs) and two insertions/deletions in both lymphomas, three SNVs unique to the donor's follicular lymphoma, and four unique to the recipient's follicular lymphoma.

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→SHOP TALK

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employers who show exemplary support of their registered oncology nurses. Moffitt recognizes its oncology nurses by rewarding those who become certified; offering two scholarships per year for nurses to attend the national ONS conference of their choice; granting three paid professional development days each year for nurses to attend professional conferences; and purchasing, using and disseminating ONS materials such as standards, guidelines, and other resources to their nurses.

"In 2011, Moffitt celebrated 25 years of oncology nursing," said **Jane Fusilero**, Vice President and Chief Nursing Officer of Moffitt. "We are honored to be recognized by the society."

THOMAS LOOK, MD

Thomas Look, MD and **Kimberly Stegmaier, MD**, both of Dana-Farber Cancer Institute, and **Adolfo Ferrando, MD, PhD**, of Columbia University Medical Center have each been named recipients of a one-year, $100,000 Bridge Grant from Alex's Lemonade Stand Foundation.

Sam Ogden

KIMBERLY STEGMAIER, MD

Look's research examines reasons for first-line therapy failure for children with T-cell acute lymphoblastic leukemia and aims to develop improved targeted therapies for this subset of high-risk patients. Stegmaier's research focuses on developing new therapies for patients with Ewing sarcoma of the bones or soft tissue surrounding bone. And Ferrando's research analyzes the role of the NOTCH1 gene in the development of T-cell ALL in order to improve targeted therapy for children with the disease.

ADOLFO FERRANDO, MD, PHD

These awards are the inaugural three Bridge Grants, which are designed to allow promising projects denied of NIH grants to continue while the researchers reapply for funding.

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→SISTER-TO-SISTER

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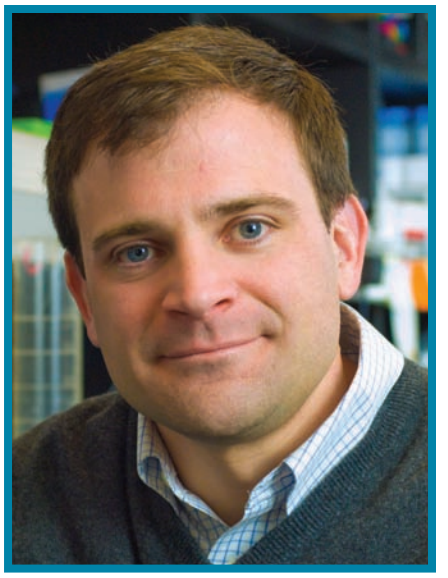
Among the identical mutations identified in both follicular lymphomas were two SNVs in BCL2, an in-frame deletion in EP300, and an in-frame insertion in KLHL6, which were recently found to be recurrently mutated in lymphoma, Weigert noted.

Among the single nucleotide variants unique to the recipient's follicular lymphoma was an ARID1A (adenine-thymine [AT]-rich interactive domain-containing protein 1A) R1276 premature stop. Loss-of-function mutations in ARID1A have been reported in solid cancers, but not yet in hematologic malignancies, Weinstock noted. On immunohistochemical staining both lymphomas had decreased ARID1A/BAF250 protein expression, suggesting that loss of ARID1A occurred through separate mechanisms in each follicular lymphoma, an indication of convergent evolution, he said.

"In fact, the donor's lymphoma was found to have a copy number loss at this locus by quantitative PCR. To determine whether the somatic mutations that we identified were present at a low frequency within the DLI, we used PCR to amplify regions flanking each mutation site from the DLI and subjected the products to ultra-sensitive deep sequencing."

NATHAN FOWLER, MD: "The authors provide an intriguing view of the genesis of follicular lymphoma…. While many oncologists recognize that follicular lymphoma typically has a slow indolent course, and occurs following characteristic mutations such as t(14;18), this paper suggests that the defining events may occur earlier than previously thought."

Eleven of the 12 SNVs and the two insertions/deletions that were identified in both lymphomas were "enriched" in the DLI—that is, they recovered at frequencies significantly above background, indicating that those mutations were present more than seven years prior to presentation of either lymphoma. All four SNVs unique to the recipient's follicular lymphoma and a mutation identified only in the donor's follicular lymphoma were not enriched in the DLI, consistent with subsequent acquisition during clonal diversification.



DAVID M. WEINSTOCK, MD: "The presence of an ancestor cell harboring many but not all mutations raises the possibility that the reason follicular lymphoma remains uncured is that the vast majority of cells are eradicated with chemotherapy but some pool of cells is not like the other follicular lymphoma cells. We may be able to identify the cells that carry some mutations and have inherent resistance to chemotherapy."

Of the final two mutations, one was detected only in the donor's follicular lymphoma and was enriched in the DLI. The other was initially detected only in the donor's follicular lymphoma, but deep sequencing recovered the mutation in 4.7% of reads from the recipient's follicular lymphoma and demonstrated enrichment in the DLI.

"The presence of a mutation in the donor's follicular lymphoma and DLI but not within the majority of the recipient's follicular lymphoma cells is consistent with at least two scenarios," Weigert continued. "Either the recipient's follicular lymphoma is derived from a clonally diversified population of ancestor cells transferred from the donor, or the mutant allele was lost in a subset or in all cells of the recipient's follicular lymphoma during clonal evolution."

Both sisters are now in remission after standard chemotherapy treatment, he said.

Key Implications

"We utilized ultra-sensitive mutation detection to elucidate the molecular ontogeny of follicular lymphoma during clonal evolution in separate hosts. This approach has broad applicability for identifying genetic variants within tumor populations that confer phenotypes like therapeutic resistance or metastatic potential."

Weinstock added that the concept of using an ultrasensitive form of detecting subclones with a specific genetic mutation offers the opportunity to use a deep sequencing approach to look for phenotypes of subpopulations. "For example, if a CML patient has a T315I mutation and we do deep sequencing, we may be able to know how many cells carry the mutation. This may possibly lead to a marker for CML patients who relapse after imatinib treatment."

The knowledge could potentially one day lead to an early treatment for follicular lymphoma, he said. "Currently, the only curative approach is stem cell transplantation, but the more we understand about the genetic aberrations that lead to follicular lymphoma, the better we'll be able to manage the disease."

Added Fowler: "The authors provide an intriguing view of the genesis of follicular lymphoma….While many oncologists recognize that follicular lymphoma typically has a slow indolent course, and occurs following characteristic mutations such as t(14;18), this paper suggests that the defining events may occur earlier than previously thought.

"Although a large percentage of the adult patient population harbors the BCL2 mutation in circulating B cells, the defining event that leads to lymphoma transformation remains elusive. The fact that both patients in this report developed the disease at the same time despite the donor being significantly immunosuppressed would suggest that either the malignant clone was able to modulate the immune microenvironment in order to allow the development of clinical disease in both patients, or the development of follicular lymphoma may be less dependent on immune competency and surveillance than hypothesized," he continued.

> The concept of a donor passing a malignancy to a recipient is well documented and considered a minimal risk to those in the transplant community. But this case gave the researchers the opportunity to understand the genetic abnormalities that led to follicular lymphoma in both cases.

"Clearly, we often observe dramatically different outcomes in patients with similar indolent lymphomas. The clues to the prognosis following treatment, including resistance to chemotherapy, will likely be found following a detailed understanding of each individual patient's genotype. Techniques that result in more sensitive detection of rare mutations will hopefully provide some of these clues."