[News * Analysis * Commentary * Controversy]

December 25, 2012 * Vol. 34 * No. 24

oncology-times.com

ONCOLOGY TIMES

Publishing for 34 Years

Lippincott Williams & Wilkins
Wolters Kluwer Health

The Independent Hem/Onc News Source

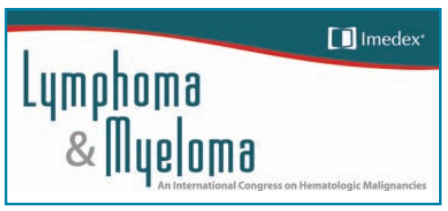
Richard Schilsky Chosen ASCO's First Chief Medical Officer: How It Came About

BY ERIC T. ROSENTHAL

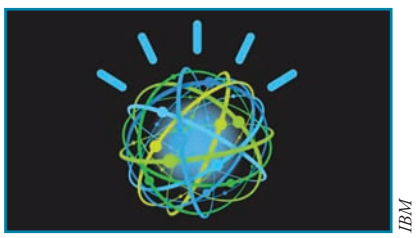
Page 8

Lymphedema: Debating Early Detection Methods pp. 18, 22

• **Palliative Care Pushing into Outpatient Settings** p. 24



• **Myeloma: 2nd Malignancies, Best Therapy for Bone Disease** pp. 30, 33



IBM

• **Using Health IT Data in New Ways** p. 29

[ALSO]

PERIODICALS

Myeloma: Second Malignancies Can Be Innate and Drug Induced

BY ROBERT H. CARLSON

NEW YORK CITY—Second primary malignancies are a known risk of treatment of multiple myeloma, and studies in the literature point the finger at certain anticancer agents. But recent research supports a hypothesis that some patients with hematologic diseases may be predisposed to second malignancies.

There is evidence that the risk of second malignancy may be related not only to therapy but also to host or disease biology, said Ola Landgren, MD, PhD, Senior Investigator in the Multiple Myeloma Section of the National Cancer Institute, speaking here at the Lymphoma & Myeloma International Congress on Hematologic Malignancies.

Concerns about second malignancies and myeloma are not new, he noted, but three clinical trials suggesting that lenalidomide might increase the risk of second primary malignancies renewed that concern, particularly for patients undergoing maintenance treatment. Research is also showing that having a plasma cell disease itself increases the risk, and there may be an additive effect from therapy.

OLA LANDGREN, MD, PHD, noted that although concerns about second malignancies and myeloma are not new, three clinical trials suggesting that lenalidomide treatment might increase the risk renewed that concern, particularly for patients on maintenance treatment. Research is also showing that having a plasma cell disease itself increases the risk, and there may be an additive effect from therapy.

Landgren said that in a study he and colleagues conducted analyzing a large Swedish database of myeloma patients and patients with monoclonal gammopathy of undetermined significance (MGUS) (***Blood 2011;118:4086-4092***), the

continued on page 31

→DATA SETS

continued from page 29

cancer registry. So we are pulling in data from these disparate sources to try to get new insights by bringing them together. For example, we might see unique patterns if we bring together the cancer registry data with the admission and discharge data.

"The ability to look across databases is actually quite important. For several years, Memorial has had a tool called Darwin, which can access data from about 1.2 million inpatients and outpatients from the last two decades stored in disparate systems.

"There is a web-based interface that allows us to build queries and draw information about patients meeting the query parameters from multiple sources such as the pathology computer and the laboratory computer.

"For example, we used the Darwin system to ask questions about patients who receive rituximab: Do they have an increased risk of developing low immunoglobulin levels, and do they have an increased risk of developing infection? This search required us to look at all patients in the pathology computer who had the diagnosis of lymphoma, all patients in the pharmacy computer who had the administration of the drug rituximab.

"We had to look in the clinical laboratory system for all patients who had immunoglobulin levels tested, and we had to look at the electronic medical record system to see how many patients were admitted for infection or treated for infection. Darwin enabled us to combine data from these disparate sources for individual patients.

IBM

"We were able to demonstrate that, in fact, patients who are exposed to rituximab have a higher risk of developing low immunoglobulin levels and that those patients have a higher risk of developing recurrent infection.

"Without Darwin, there was no simple way to do this because it required us to pull data from so many different sources and then integrate them."

How do Memorial's own datasets compare with the brain of Watson?

"The physician in charge of the Watson effort is Mark Kris, a lung cancer specialist here at Memorial. Watson is a massively parallel computer that can take multiple streams of information and try to understand them. The heart and soul of Watson is that it can read and interpret natural language. So if you give it a book, it can read the book and actually understand the book, to some extent.

"But Watson does not know how to synthesize information. That is what the collaboration with Memorial is all about. Watson actually has already read more of the world's literature about cancer than any human would ever be able to read in multiple lifetimes. As a result, Watson has a lot of book knowledge, but book knowledge is not necessarily clinical acumen. The Memorial input is to take experts in the field and basically develop algorithms that say, 'This is actually how we use the data; this is how we value data.'

"But this is more than just embedding the expert. We actually learn from Watson as well because Watson has read more than we have. So it might sometimes come up with a recommendation that we have to say, 'Is that the right thing it's recommending based on what it knows? Or do we have to tweak the algorithm because it actually made the wrong suggestion?' Sometimes it will make a suggestion that we will say, 'Oh, that is the right suggestion' even though it is a surprise to us."

When will Watson's expertise be available to oncologists outside Memorial?

"The hope is that within a couple of years, there will be a workable version. What might happen is that the Watson advisor—or whatever it is called by then—would be initially restricted to address metastatic lung cancer or adjuvant breast cancer and a few other diagnoses. But if it's a different clinical situation, you have to wait until the next iteration where that clinical situation is appropriate.

"Obviously the approach is to take the most important clinical situations and implement them first. As we go forward, we will add the less common clinical situations or those clinical situations in which Watson will have less of an impact on outcome."

iPad Exclusive!

PODCAST: Listen on the iPad edition of this article as **Andrew Zelenetz, MD, PhD**, Chief of the Lymphoma Service and Vice Chair of Medical Informatics at Memorial Sloan-Kettering Cancer Center, describes how oncologists are training the Watson computer—and how that work will help cancer patients beyond Memorial.

OT Broadcast News

To receive our iPad issues, download the free Oncology Times app from the App Store today! Visit **http://bit.ly/OT-iPadApp**, *search in the App Store, or follow the link on* **oncology-times.com**

→MYELOMA-2ND MALIGNANCIES

continued from page 30

incidence of acute myeloid leukemia and myelodysplastic syndrome increased in both myeloma and MCUS patients compared with that in the general population.

"IgG/IgA MGUS patients had an increased risk of AML/MDS, but IgM MGUS patients did not, and the greatest risk was among MGUS patients with M-protein concentrations greater than 1.5 g/dL," he said. "This doesn't prove there is a relationship, but it highly suggests there is some disease-related underlying risk, because none of these patients had received therapy."

And ongoing research at the NCI is finding evidence of myeloid abnormalities at baseline in patients with smoldering myeloma in the absence of exposure to therapy, pointing to some kind of precursor MDS, he said.

Discuss Risk with Patients

"For the group of patients where these second cancers happen, it is devastating," Landgren said. "The good thing is, it is very unlikely to happen."

He said clinicians should tell patients the facts—that there are plusses and minuses, that treating with lenalidomide has been found in three trials to prolong the time before the disease gets active again, but that unfortunately, there is an increased risk for second malignancy—"The tradeoff has to be discussed with the patient."

The three randomized myeloma studies suggesting a link between lenalidomide and second malignancy were presented at the 2010 American Society of Hematology Annual Meeting. The European IFM 2005-02 study by Attal and colleagues—subsequently published earlier this year in the *New England Journal of Medicine* (***2012;366:1782-1791***) showed that lenalidomide maintenance after stem-cell transplantation significantly prolonged progression-free and event-free survival compared with placebo.

But the incidence of second primary hematologic cancers was 4.2 percent in the lenalidomide group versus 1.7 percent in the placebo group, and the incidence of patients with at least one second primary cancer was 8.5 vs. 3.6 percent, respectively.

In the second study, the CALGB 100104 trial by McCarthy et al (***NEJM 2012;366:1770-1781***) studied lenalidomide maintenance therapy after stem-cell transplantation. The treatment group had significantly longer time to progression and significantly increased overall survival, but treatment was associated with a rate of second primary hematologic cancers of 3.5 vs. 0.4 percent for placebo.

And in the MM-015 trial by Palumbo and colleagues (***NEJM 2012;366:1759-1769***), progression-free survival more than doubled for patients with newly diagnosed myeloma ineligible for transplantation who received lenalidomide maintenance. But the three-year rate of invasive second primary tumors was seven percent in the two lenalidomide-treated groups vs. three percent without lenalidomide.

Wrong Culprit?

Still, meeting co-chair Ruben Niesvizky, MD, Director of the Multiple Myeloma Service at New York Presbyterian Hospital-Weill Cornell Medical Center, said he thought concern about second malignancies and lenalidomide is being overstated.

"I think the culprit is genotoxic therapy such as melphalan, doxorubicin, etoposide, and cisplatin—all those drugs cause leukemia and secondary cancers," he said in an interview. "The deleterious effect of lenalidomide and the development of secondary malignancies have not been seen in individuals who take just lenalidomide."

Similarly, meeting chair Morton Coleman, MD, Clinical Professor of Medicine and Director of the Center for Lymphoma and Myeloma at New York Presbyterian Hospital-Weill Cornell Medical Center, said he believes that in some patients a predisposition for myeloproliferative diseases could be fueled by alkylating agents.

"Some myeloma patients have some element of myelodysplasia, and if you give an alkylator with Revlimid [lenalidomide] you just uncover more of that predisposition," he said in an interview. In those second malignancies, use of lenalidomide is usually in combination with or following the use of alkylating agents—"It looks like it's not just Revlimid, but rather Revlimid with an alkylating agent."

He said his institution has a study with BiRD (biaxin-Revlimid-dexamethasone), which does not use alkylating agents—"And we haven't seen a preponderance of second malignancies, with the exception perhaps of some skin malignancies."

Even so, things need to be kept in perspective, he said: Regardless of whether Revlimid is or is not used, the incidence of second malignancies does not have a major impact on overall survival. "Everything is a risk-vs-benefits ratio. If you can make a compelling case for using maintenance Revlimid, I think you might get more hematologic malignancies, but it really doesn't matter in terms of the overall survival of the patients."

On the other hand, he said, a case might be made for using another agent such as bortezomib instead of lenalidomide in patients who have had alkylators.

Ongoing research at the NCI is finding evidence of myeloid abnormalities at baseline in patients with smoldering myeloma in the absence of exposure to therapy, pointing to some kind of precursor MDS.