

OncoLog

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New Drugs Control Symptoms of Myeloproliferative Disorders and Improve Quality of Life for Patients

By Bryan Tutt

Recent clinical trials have demonstrated that a new class of drugs can effectively treat myeloproliferative disorders.

These disorders are a diverse group of diseases in which the blood-producing cells in the bone marrow start to grow without control and function abnormally.

Myeloproliferative disorders can be classified into two main categories according to the presence or absence of the Philadelphia chromosome abnormality, which can be identified by bone marrow karyotyping.

“Any patient who has the Philadelphia chromosome abnormality—a translocation between chromosomes 9 and 22—in the bone marrow cells is considered to have chronic myelogenous leukemia,” said Srdan Verstovsek, M.D., Ph.D., an associate professor in the Department of Leukemia at The University of Texas MD Anderson Cancer Center. “None of the other myeloproliferative disorders can be identified by a specific test.”

The three main Philadelphia chromosome–negative myeloproliferative disorders—polycythemia vera, essential thrombocythemia, and primary myelofibrosis—are sometimes referred to as the classic myeloproliferative disorders, and they are most often diagnosed in patients aged 60–70 years. Patients with any of these disorders may experience disease progression over time. For example, patients with polycythemia vera or essential thrombocythemia can develop secondary myelofibrosis, called post-polycythemia or



Dr. Srdan Verstovsek examines a patient whose symptoms from myelofibrosis improved during his participation in a clinical trial of a JAK2 inhibitor.

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Myeloproliferative Disorders

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post-thrombocytopenia myelofibrosis. Also, any of the three classic myeloproliferative disorders can progress to acute myelogenous leukemia.

Complications from myeloproliferative disorders

Patients with essential thrombocythemia, characterized by excess platelet production, have a normal life expectancy in general, although they face an increased risk of blood clots that may affect their quality of life. Each year, 6,000–7,000 new cases of essential thrombocythemia are diagnosed in the United States.

In patients with polycythemia vera, an abnormal proliferation of all hematopoietic bone marrow elements increases the total blood volume. The main complication this causes for patients is a high red blood cell count, which leads to increased clotting similar to that caused by essential thrombocythemia. Patients with polycythemia vera have a somewhat shorter life expectancy than is normal for their age group. Polycythemia vera has about the same incidence rate as essential thrombocythemia.

Primary myelofibrosis is less common than the other two classic myeloproliferative disorders. Each year, about 3,000 people in the United States are diagnosed with myelofibrosis, including patients with post-polycythemia and post-thrombocytopenia myelofibrosis (who account for up to a quarter of all patients with myelofibrosis). In patients with myelofibrosis, bone marrow cells grow without control, and the bone marrow stromal cells react by secreting a number of different proteins that lead

to the formation of fibers in the bone marrow. This scarring prevents the bone marrow from being able to produce enough blood cells.

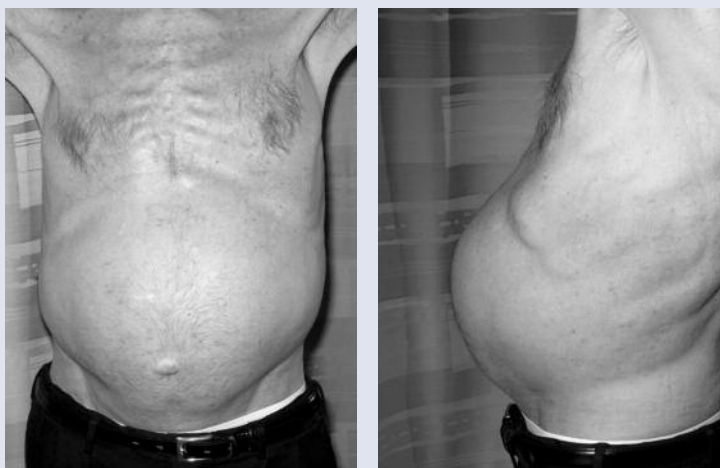
As the body tries to compensate for the lack of red blood cells produced by the bone marrow, the spleen enlarges and contributes to the production of blood cells. Abnormal blood cells can also infiltrate the spleen and other organs (e.g., the liver). As a result, spleen enlargement occurs in about 80% of patients with myelofibrosis. These patients' spleens may double or even triple in size. The liver is enlarged in about 40% of myelofibrosis patients.

Fatigue is the most common symp-

tom of myelofibrosis. Many myelofibrosis patients also experience decreased appetite, weight loss, and malnutrition as a result of the enlarged spleen pressing on the stomach. These patients tend to have decreased performance status and poor quality of life. As the disease progresses, patients may have increasing weakness, progressive enlargement of the liver and spleen, liver failure, portal hypertension causing bleeding in the gastrointestinal tract, pulmonary hypertension, lung failure, and cardiac failure. "Most of these patients die from body wasting, organ failure, and similar disease complications within 5–7 years," Dr. Verstovsek said. About 20% of cases of myelofibrosis progress to acute myelogenous leukemia, he added, and the average patient survival after such progression is only 5 months.

Atypical myeloproliferative disorders include hypereosinophilic syndrome (an excess number of eosinophils in the

blood and bone marrow) and systemic mastocytosis (an infiltration of mast cells into non-skin tissues). Eosinophilic infiltration of the organs is a potentially deadly characteristic of hypereosinophilic syndrome. Mastocytosis is usually confined to the bone marrow and may be indolent or aggressive. Because eosinophils and mast cells are part of normal allergic reactions, patients with hypereosinophilic syndrome and systemic mastocytosis experience allergic reactions and skin rashes. Both of these disorders tend to affect patients in their 40s. "These disorders are very rare," Dr. Verstovsek said. "Nobody has a good data base of these patients, and



▲ **ABOVE:** Photos of a patient before therapy with an experimental JAK2 inhibitor show the distended abdomen caused by the enlarged spleen, a common symptom of myelofibrosis.

▼ **BELOW:** Photos taken after 2 months of therapy with a JAK2 inhibitor show a marked reduction in the patient's splenomegaly.



it is believed that there are only a few thousand people living with these diseases in the United States.”

Treatment

Systemic mastocytosis and hypereosinophilic syndrome are usually managed with prednisone or other steroids, while hydroxyurea or other chemotherapeutic agents may be used to treat more aggressive cases.

For chronic myelogenous leukemia, imatinib is the first-line treatment, and phase III trials demonstrating the effectiveness of two newer drugs—dasatinib and nilotinib—were described in the August 2010 issue of *OncoLog*.

Treatment of the three classic myeloproliferative disorders varies. In patients with polycythemia vera, phlebotomies are used to reduce the red blood cell count. This is typically done every 2 weeks until the patient’s hematocrit is stabilized at below 45%, after which phlebotomies are done as needed. Low-dose aspirin is given to reduce clotting in patients with polycythemia vera and in those with essential thrombocythemia. Patients with either of

these disorders who are at high risk for clotting may also receive hydroxyurea to decrease elevated blood cell counts.

There are no treatments approved by the U.S. Food and Drug Administration for myelofibrosis, but medications prescribed off-label for its treatment include hydroxyurea, thalidomide, lenalidomide, steroids, and growth factor injections. Low-intensity stem cell transplantation is also used to treat myelofibrosis, but this is considered risky, resulting in death in about 15% of patients.

None of these treatments for myelofibrosis has been found to be both safe and effective, and none has been proven to change the natural course of the disease. However, recent studies have shown the effectiveness of a new class of drugs in patients with the three classic myeloproliferative disorders.

JAK2 inhibitors

In 2005, researchers discovered a mutation in the *JAK2* gene that occurs in about 80% of patients with the three main Philadelphia chromosome–negative myeloproliferative disorders. The *JAK2* gene produces an enzyme that is

inside all cells, attached to receptors for blood growth factors that signal the production of blood cells. In patients with the mutation, the *JAK2* enzyme is produced even when the receptors are not activated by blood growth factors, causing abnormal cell growth. Several drugs have been developed to inhibit the activity of the *JAK2* enzyme.

So far, eight *JAK2* inhibitors have been tested in clinical studies in patients with primary or secondary myelofibrosis. Dr. Verstovsek has been the lead investigator for trials of most of these drugs. He and his colleagues recently published in the *New England Journal of Medicine* the results of a phase I/II trial of the *JAK2* inhibitor INCB018424 in patients with myelofibrosis. Half the patients in the study had their enlarged spleens reduced by about 50%. Another quarter of the patients had their spleens reduced by 25%. The spleen reduction improved the patients’ appetites, and other general symptoms such as fatigue and weakness improved as well. Patients gained weight and were able to

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CLINICAL TRIALS: Myeloproliferative Disorders

The following clinical trials of treatments for myeloproliferative disorders are available at MD Anderson. A more complete list is available at www.mdanderson.org/oncolog.

■ A Phase II, Prospective, Open-Label Study (PO-MMM-PI-0011) to Determine the Safety and Efficacy of Pomalidomide (CC-4047) in Subjects with Primary, Post-Polycythemia Vera, or Post-Essential Thrombocythemia Myelofibrosis (2007-0199).

Principal investigator (PI): Srdan Verstovsek, M.D., Ph.D. The main goal of this study is to learn whether CC-4047 can help to control myelofibrosis with myeloid metaplasia. The safety of this drug will also be studied.

■ A Phase I/II, Open-Label Multi-Center Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of the JAK2

Inhibitor AZD1480 Administered Orally to Patients with Primary Myelofibrosis and Post-Polycythemia Vera/Essential Thrombocythemia Myelofibrosis (2009-0067).

PI: Dr. Verstovsek. The primary goal of this study is to learn whether AZD1480 is safe when given to patients with myelofibrosis. The secondary goal is to learn whether AZD1480 can help to control the disease.

■ A Phase I Study of LY2784544 in Patients with JAK2 V617F-Positive Myeloproliferative Disorders (2010-0167).

PI: Dr. Verstovsek. The goal of this study is to find the highest tolerable dose of LY2784544 that can be given to patients with myeloproliferative disorders.

■ Randomized, Open Label, Multi-center Phase III Study of Efficacy and Safety in Polycythemia Vera Subjects

Who Are Resistant to or Intolerant of Hydroxyurea: JAK Inhibitor INC424 Tablets Versus Best Available Care (the RESPONSE Trial) (2010-0808).

PI: Dr. Verstovsek. The goal of this study is to compare the efficacy of INC424 (also called INCB018424) to best available therapy as assessed by both the absence of phlebotomy and reduction in spleen volume.

■ A Phase I/II Multiple Ascending Dose Study to Evaluate the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of BMS-911543 in Subjects with Myelofibrosis (2010-0782).

PI: Dr. Verstovsek. This study will assess the safety, tolerability, dose-limiting toxicities, and efficacy of BMS-911543. ■

FOR MORE INFORMATION

Visit www.clinicaltrials.org.



Compass

Quarterly discussion of cancer types for which there is no standard treatment or more than one standard treatment

Metastatic Melanoma

Experimental treatments could be preferable to standard therapies for metastatic melanoma

By **Sunni Hosemann**

Introduction

Melanomas, which arise from melanocytes, are the most aggressive form of skin cancer.

Fortunately, most melanomas are discovered at an early stage when they are highly curable by surgery alone. According to data from the U.S. Surveillance, Epidemiology, and End Results program, 84% of cutaneous melanomas are discovered while localized, and for these patients, the 5-year relative survival rate is 98%.

Patients whose melanoma has spread to regional lymph nodes (stage III; about 8% of cases) have a 5-year relative survival rate of about 62%, and patients whose cutaneous melanoma is unstaged at diagnosis (about 4% of cases) have a 5-year relative survival rate of 76%. Patients who present with metastatic disease (stage IV; about 4% of cases) have a 5-year relative survival rate of only about 16%.

Types of melanoma

Although most melanomas occur on the skin surface, approximately 7% of primary melanomas are noncutaneous, according to Scott Woodman, M.D., Ph.D., an instructor in the Department of Melanoma Medical Oncology at The University of Texas MD Anderson Cancer Center. Noncutaneous melanomas occur most often in the eye and mucous membranous sites such as the anus, rectum, vulva, vagina, nasal sinuses, and mouth. These tumors are associated with poorer prognoses than are cutaneous melanomas.

Noncutaneous melanomas tend to go undetected until they reach an advanced stage because they are hidden deep in the eye or in mucosa, where they cause no early symptoms. These locations also offer access to relatively rich vascular and/or lymphatic environments, enabling noncutaneous melanomas to spread more quickly than their cutaneous counterparts. Furthermore, genetic differences between cutaneous and noncutaneous melanomas cause them to have different biological behaviors and to respond differently to treatment.

According to Kevin Kim, M.D., an associate professor

in the Department of Melanoma Medical Oncology, even cutaneous melanomas can differ significantly depending on where on the skin they occur and the degree of sun damage to the skin. In addition, the invasiveness of cutaneous melanomas may vary according to histological subtype; nodular melanomas are more invasive—and therefore more aggressive—than are superficial spreading, lentigo, and acral lentiginous melanomas. “Melanoma is not a single entity,” Dr. Kim said, “and this means that more tailored treatments are needed.”

Standard treatment options

“The average survival for patients with stage IV metastatic melanoma is 6–10 months,” said Michael Davies, M.D., Ph.D., an assistant professor in the Department of Melanoma Medical Oncology, “and this hasn’t changed for 30 years.”

The current standard treatment for metastatic melanoma is chemotherapy with dacarbazine, which has been shown to shrink tumors in only 10%–15% of patients who receive it. Unfortunately, this effect rarely persists more than a few months as chemoresistance develops. “In short, even though dacarbazine’s toxicity is relatively mild and the drug may prolong survival by a short time for a few patients, it’s not much better than supportive care for the majority of patients with metastatic melanoma,” Dr. Davies said.

High-dose bolus interleukin-2 (IL-2) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of metastatic melanoma in 1998. IL-2 is an immunomodulatory agent that acts by stimulating the immune system to attack the cancer cells. IL-2 has been shown to achieve rates of tumor reduction similar to those with dacarbazine, but about half the patients who respond to IL-2 have a complete response—a durable disease remission for more than 10 years. Most patients who achieve a complete response subsequently remain free of melanoma for the rest of their lives. However, according to Dr. Davies, IL-2 is among the most toxic of cancer treatments, with marked side effects and a significant risk of life-threatening adverse events. For these reasons, treatment with high-dose IL-2 requires hospitalization in a cardiac monitoring or intensive care setting at a center experienced in the agent’s administration, with cardiopulmonary specialists available. Despite these precautions and the use of IL-2 being limited to patients with excellent health and functionality, the treatment itself has a 1%–2% mortality rate.



Michael Davies, M.D., Ph.D.
Assistant Professor,
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Kevin Kim, M.D.
Associate Professor,
Melanoma Medical
Oncology



Scott Woodman, M.D., Ph.D.
Instructor, Melanoma
Medical Oncology

“IL-2 is a wonderful treatment for those patients who are able to achieve a complete response and may therefore be cured of this aggressive disease,” Dr. Davies said. “Unfortunately, however, we don’t yet know how to identify those rare patients who have the best chance to benefit from this highly toxic treatment.”

Currently, IL-2 treatment can be considered only for patients who are in otherwise excellent health and only after extensive discussion of the risks and benefits of this treatment. Patients with brain metastases should be monitored with extra caution while receiving IL-2 because of the potential for edema at the tumor sites and because historical data reveal particularly low response rates to IL-2 in these patients.

Interferon alfa-2b—which, like IL-2, is an immunotherapy agent—is approved by the FDA as an adjuvant treatment for patients with stage II melanoma and primary tumors more than 4-mm thick or with stage III melanoma. Interferon alfa-2b has been shown to delay recurrence in these patients, but in most clinical studies it has not improved overall survival durations. Current studies are exploring whether interferon alfa-2b could be effective against metastatic melanoma if used in combination with chemotherapeutic agents or new immunotherapies.

Like IL-2, interferon alfa-2b involves a challenging and lengthy treatment. Interferon therapy consists of an induction phase requiring intravenous infusions five times a week for 4 weeks followed by a 48-week course of subcutaneous injections three times a week. This treatment is associated with a variety of side effects, such as flu-like symptoms, liver toxicity, and psychiatric disturbances. “With the questionable benefits of interferon therapy for improving survival in patients,” Dr. Davies said, “the side effect profile and quality of life are important considerations for patients and physicians.”

Clinical trials

Because of the limited survival benefits from the FDA-approved treatments, most experts agree that clinical trials are the best option for patients with metastatic melanoma. However, even in clinical trials, progress has been slow. Not only have some promising approaches failed, but because metastatic melanoma is relatively uncommon, there have been few large, randomized trials. Nevertheless, investigators strive to develop treatment approaches that have the greatest chance of success, building upon research that has provided an improved understanding of the molecular underpinnings of melanoma.

“We want to be able to match the right patients with

the right treatments,” Dr. Davies said. To make this possible, researchers at MD Anderson and other institutions have been working to identify the molecularly defined subtypes of melanoma and the ideal treatment for patients in each group.

According to Dr. Woodman, researchers have recently identified key genetic mutations in melanoma. “This is important because it provides us with the opportunity to target these tumors with specific agents,” he said.

Approximately 60% of patients with cutaneous melanomas have mutations in the *BRAF* gene. These mutations occur most frequently in tumors arising from skin surfaces with intermittent sun damage. Another 20% of cutaneous melanomas have *NRAS* mutations (which exclude *BRAF*). There are fewer *BRAF* mutations in tumors arising from non-sun-damaged areas of the skin (i.e., palms of hands, soles of feet), from chronically sun-damaged skin, and from mucosal sites. Mutations in the *KIT* gene are found in some of these less common melanomas, including mucosal and acral melanomas.

The identification of *KIT* mutations in these subtypes of melanoma has led to multiple ongoing phase II clinical trials in which melanoma patients are treated with FDA-approved agents that inhibit activated *KIT* in other cancers. For example, Drs. Kim and Woodman have designed a novel phase II trial to test the molecular effect of dasatinib in patients with mucosal and acral melanoma.

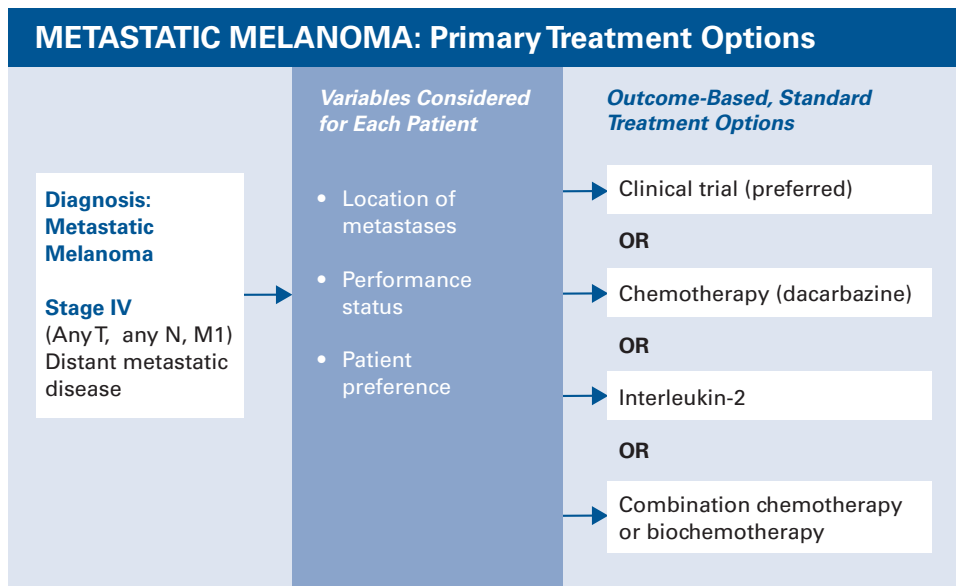
Other studies are under way to test experimental agents that target the mutant *BRAF* protein in patients with melanoma. PLX4032, an oral medication that selectively and potently inhibits the most common *BRAF* mutation, achieved clinical responses in more than 80% of patients with stage IV or unresectable stage III melanoma in a recent phase I clinical trial. “These results are unprecedented,” Dr. Davies said. “When you consider that the FDA-approved therapies for metastatic melanoma achieve clinical responses in only 10%–15% of patients, this trial demonstrates the dramatic potential of personalized, targeted therapies to revolutionize the treatment of this disease.” The results of the trial supported the specificity of PLX4032 for the mutant *BRAF* protein, as no patients who had a normal *BRAF* gene responded to the medication. The treatment was extremely well tolerated; a rash was the most common side effect. Phase II and III trials of PLX4032 are under way.

In early studies of another *BRAF* inhibitor, GSK2118436, researchers have reported similar efficacy and toxicity to that of PLX4032. While the clinical activity and limited toxicity of these targeted therapies are promising, investigators are working to improve these treatments further.

Some patients have developed new cancers of the skin as a side effect of the BRAF inhibitors. Although these tumors—which were not melanomas—were controlled with surgical removal and have not required any responding patient to discontinue BRAF inhibitor therapy, investigations are ongoing to understand why these tumors develop and how to prevent them. Another concern is that although the overwhelming majority of melanoma patients with BRAF mutations who have received BRAF inhibitors initially responded to the medication, most patients eventually develop clinical resistance to the drugs, and their tumors start growing again. “Resistance appears to develop in some patients after 7–8 months,” Dr. Davies said, “so we are looking into why that might be and considering ways to make the effects last, perhaps with combinations.”

There are a variety of combinatorial approaches being considered to combat resistance to the BRAF inhibitors, including the addition of targeted therapies against other pathways that may be activated concurrently with BRAF. Other combinations might include agents with completely different mechanisms of action, such as immunotherapy agents. Ipilimumab, a monoclonal antibody, activates T cells and has shown promise against metastatic melanoma when used alone and in combination with vaccine therapy. In a phase III trial comparing ipilimumab to the GP100 peptide vaccine in patients whose metastatic melanoma had not responded to first-line treatments, the average survival duration increased from 6 months to 10 months. “It was the first time in melanoma that an experimental drug increased survival over the control drug,” said Dr. Kim, who believes ipilimumab may have a role in future combination therapies. While ipilimumab does have the potential to cause autoimmune side effects, it does not pose the same acute cardiovascular risks as IL-2; therefore, ipilimumab can be administered safely as an outpatient treatment and potentially made available to more patients than is IL-2.

Another immune-based approach, adoptive T cell therapy, is being developed at MD Anderson under the direction of Patrick Hwu, M.D., a professor in and chair of the Department of Melanoma Medical Oncology. Dr. Kim explained that the therapy involves harvesting T cells from the patient’s tumor. The T cells are multiplied in the laboratory, and then billions of the cells are transfused back into the patient. These T cells specifically target the tumor but are not numerous or strong enough to eradicate it. To help these tumor-specific T cells proliferate in the bloodstream, patients are given chemotherapy to deplete ordinary T cells prior to



the tumor-specific T cells’ reintroduction and given high-dose IL-2 to stimulate T cell growth after the T cells’ reintroduction. “Nearly 50% of patients with metastatic melanoma have had a clinical response to adoptive T cell therapy so far,” said Dr. Kim, who added that the therapy is still experimental.

These avenues of research represent important advances for patients with metastatic melanoma, for whom the current standard treatments have been woefully ineffective and/or highly toxic.

“This is a very exciting time in the history of a disease for which there have been few options,” said Dr. Woodman. “I’m optimistic that the treatment choices in 5–10 years will be very different than the ones I’ve seen thus far in my career as an oncologist.” ■

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Breast Awareness

Guidelines recommend breast awareness rather than formal self-exams

“I don’t do breast self-exams because I don’t know how.”

That’s what many doctors used to hear from women. But updated guidelines are assuring women that they will know if something is wrong with their breasts and enabling women to be involved in their own breast health. Today, doctors believe that instead of conducting a standardized self-examination, women should practice breast awareness by being familiar with how their breasts look and feel and reporting any changes to their doctor immediately.

Awareness versus self-exam

The University of Texas MD Anderson Cancer Center no longer recommends that women follow a formal technique in checking their breasts for suspicious lumps or changes—a practice called a breast self-exam. Research has not shown a benefit for women in finding breast lumps by following a formal technique.

In fact, many breast cancer patients at MD Anderson found a breast lump or other symptom of breast cancer when they were going about everyday activities, such as showering or dressing.

Many breast cancer survivors noticed a lump or other change in a breast during routine activities like bathing or dressing.

Indeed, breast awareness does not require special training—women just need to know their own bodies. MD Anderson recommends that women be familiar with the look and feel of their breasts—and that there’s no right or wrong way to do that. Touching can range from informal touching, such as in the shower, to conscious touching to feel for any changes.

Frequently asked questions

How do I know if my breast feels different?

It’s common to wonder whether you’d recognize a breast change. Generally, if you can’t tell whether you have a change in your breast, there probably hasn’t been a change.

For example, while bathing you would notice a new lump that had arisen on your calf. If you had played soccer that day, you would probably assume you had been kicked. But if there were no logical reason for the lump to be there or if the lump lasted more than a few days, you would tell your doctor immediately. The same is true for breast awareness: if something is strange or new and doesn’t have a good explanation, don’t hesitate to contact your doctor.

What kind of changes should I look for?

Many changes aren’t cancer, but here are some changes to look for. If you notice any of these changes—or even a breast change not on this list—and it lasts for more than 2 weeks, tell your doctor promptly:

- Lump or mass in your breast
- Enlarged lymph nodes in the armpit
- Changes in breast size, shape, skin texture, or color
- Skin redness
- Dimpling or puckering
- Nipple changes or discharge
- Scaliness
- Nipple pulling to one side or a change in direction ■

FOR MORE INFORMATION

- Talk to your physician
- Visit www.mdanderson.org
- Call askMDAnderson at 877-632-6789



Breast Awareness Online Resources

MD Anderson Breast Self Awareness Patient Education Brochure:

<http://www2.mdanderson.org/app/pe/index.cfm?pageName=openDoc&docid=2338>

Susan G. Komen for the Cure:

<http://www5.komen.org/BreastCancer/Breastselfawareness.html>

American Cancer Society:

<http://www.cancer.org/Cancer/BreastCancer/>

ADDRESS SERVICE REQUESTED

Myeloproliferative Disorders

[Continued from page 3]

walk more. The most common adverse effect was myelosuppression, which occurred in less than 10% of the patients.

A phase III placebo-controlled study of INCB018424 in patients with myelofibrosis was recently conducted at MD Anderson and other centers, and the results will be available soon.

“Clinically, with JAK2 inhibitors we see good control of the signs and symptoms of myelofibrosis in the majority of patients,” Dr. Verstovsek said. “Some of my patients whose activities had been severely limited by fatigue and weakness have experienced marked improvement and said they’re able to go dancing or play golf again.”

In another phase II study led by Dr. Verstovsek, INCB018424 was given to patients with hydroxyurea-resistant or hydroxyurea-refractory polycythemia vera. Dr. Verstovsek was amazed by the results: all but one patients’ hematocrit decreased to below 42%, a goal of therapy. On the basis of these results, a phase III study of INCB018424 in patients with polycythemia vera has been approved. “I suspect that in a year or so we might be talking about this drug being a very effective, approved therapy for both myelofibrosis and polycythemia vera,” Dr. Verstovsek said.

Importantly, JAK2 inhibitors are not specific to the mutated JAK2 enzyme; they inhibit the activity of the normal JAK2 enzyme as well. This means that patients with Philadelphia chromosome–negative myeloproliferative disorders are likely to

benefit from JAK2 inhibitors regardless of whether they have a JAK2 mutation.

“When the JAK2 mutation was first discovered, we thought it was the cause of these disorders,” Dr. Verstovsek explained. “We now know of at least eight other mutations that are present in patients with myeloproliferative disorders and can cause the activation of the JAK2-initiated intracellular signalling cascade of proteins that leads to the abnormal cell growth. Multiple mutations can be present in the same patient, but clinically these patients present in the same way regardless of their mutation profile.”

Because JAK2 inhibitors affect normal JAK2 production, the drugs cannot be given in doses sufficient to completely eliminate myeloproliferative disorders because that would completely suppress normal blood cell growth. Long-term follow-up of the patients in the recently completed studies and in ongoing studies will determine whether JAK2 inhibitors prolong patients’ lives. However, the studies have already shown that JAK2 inhibitors can improve patients’ quality of life and reduce their symptoms. These drugs are currently available only in clinical studies, so Dr. Verstovsek urges doctors to make these studies known to their patients with any of the three classic myeloproliferative disorders. ■

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