OncoLog
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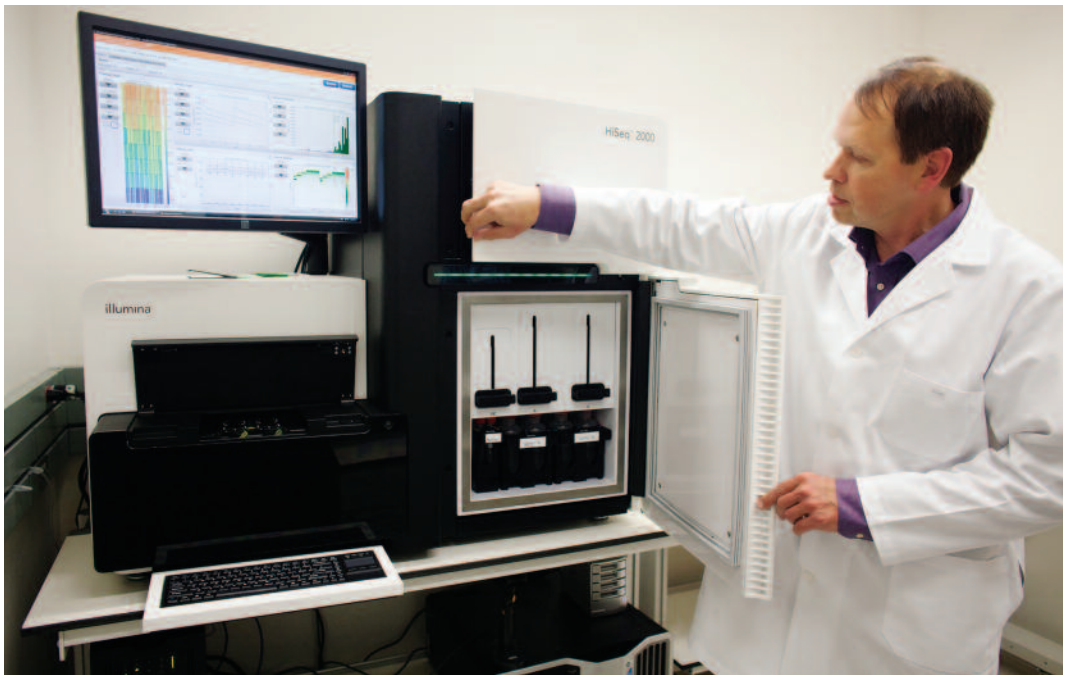
Advances in Gene Mapping Technology May Accelerate Cancer Drug Development

By Bryan Tutt

As new technology makes DNA sequencing faster and less expensive, researchers aim to exploit these abilities to develop novel targeted cancer therapies.



Dr. Alexei Protopopov, an associate director at the Institute for Applied Cancer Science, demonstrates a DNA sequencing machine. Technological advances have reduced the time and cost of sequencing a human genome, improving researchers' ability to develop experimental drugs that target cancer-causing mutations.

"It took about 10 years to get the first human genome sequenced," said Giulio Draetta, M.D., Ph.D., a professor in the Department of Genomic Medicine and the director of the Institute for Applied Cancer Science at The University of Texas MD Anderson Cancer Center. "When the Human Genome Project's work was conducted in the 1990s, they had huge rooms with sequencers, one next to another—these machines read along the DNA sequence to be able to divine the nucleotides that emerged; these nucleotides were then assembled together." Systems are now available that can sequence a human genome in less than a week with a single machine, and even faster machines are being developed.

Genetic information and cancer

The information obtained from DNA sequencing is affecting cancer research in

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three main areas, according to Dr. Draetta.

First, mutations that affect cancer cells' sensitivity to treatment have been identified. "Some emerging treatments are based on mapping the genome to look for mutations that respond to certain drugs," Dr. Draetta said. For example, the melanoma drug vemurafenib specifically targets the *BRAF* V600E mutation and is approved by the U.S. Food and Drug Administration for the treatment of melanomas with such mutations. And non–small cell lung cancers with particular mutations to *EGFR* are sensitive to gefitinib and erlotinib.

Second, genetic information has revealed common themes in cancer cells that explain their resistance to treatment. "Most tumors inactivate certain mechanisms that induce cell death. The tumors tend to survive even if you bang them with radiation therapy or chemotherapy," Dr. Draetta said. "We can develop all sorts of therapies, but there is resistance because tumors don't want to die. Now, at the genome scale, we know that these mechanisms that induce cell death are the predominant mechanisms of resistance that we have to deal with."

Finally, DNA sequencing has revealed a greater extent of heterogeneity among cancer genomes than was once thought. A recent paper in the *New England Journal of Medicine* (2012; 366:883-892) described different mutations found in biopsy specimens from primary tumors and different metastatic sites in the same patients. The implication of this finding is that an agent that targets a specific mutation might be effective against a patient's primary tumor but ineffective against metastases.

"The idea had always been that a tumor originates from a single mutated cell and that as it expands every cell in the tumor is the same. The reality is that cancer cells keep mutating as they move around the body," Dr. Draetta said. "This makes the task of curing cancer daunting, but I like to believe that knowledge is power.

> **"The more we learn about the complexity of tumors, the more we can look for common themes or a common root cause."**
>
> **– Dr. Giulio Draetta**

The countermeasure to this problem of heterogeneity is to find commonality. The more we learn about the complexity of tumors, the more we can look for common themes or a common root cause."

A new approach to drug development

DNA sequencing technology is a contributing factor to what Dr. Draetta described as a paradigm shift in the approach to drug development. This new research paradigm seeks to bridge gaps that are not always addressed, or are not addressed quickly, by academic research centers and pharmaceutical companies working separately.

"Academic institutions have traditionally pursued research on an individual basis. A particular scientist might be interested in curing a particular disease—and once the scientist has published reports, pharmaceutical companies have developed drugs based on the research," said Dr. Draetta, who has led research laboratories in both settings. He pointed out that the traditional approach makes it difficult for pharmaceutical companies to invest in research for therapies that target a specific mutation found in a small subset of cancer patients.

"Drugs like blood pressure medication, which many patients may take every day for 20–30 years, are profitable for pharmaceutical companies and enable them to invest in research," Dr. Draetta said. "But the companies have realized that they are not going to make that kind of money with a single targeted oncology drug because the complexity of cancer makes it unlikely that a single drug will be used to treat a large number of patients."

At MD Anderson's Institute for Applied Cancer Science, research teams work to identify targets for new drugs and then develop the drugs themselves. So far, the institute has about 70 research professionals from such fields as medicinal chemistry, pharmacology, genomics, bioinformatics, biology, and biochemistry. These professionals are divided into eight teams that work simultaneously on different aspects of multiple projects.

Dr. Draetta said the ability to quickly sequence a cancer genome makes the collaboration between work groups possible. "We can immediately go back and look at gene databases and ask, 'Is this gene really altered? Which subtype of breast cancer is it? Can we find cancer cell lines that carry this alteration?' Then we can study those cell lines and make sure there is dependency on the mutation," he said. Dr. Draetta explained that the fact that a gene is amplified does not mean that the cancer needs it to survive. The cancer may have needed the mutation at one point, but additional mutations can make the first mutation redundant. Genomic information helps identify such mutations as unlikely therapeutic targets before drugs are developed.

"Each team is working on a specific time line to make sure a drug candidate's mechanism of action is valid before it goes to clinical trials," Dr. Draetta said. "The idea is to make sure there are no obvious mechanisms of resistance to a particular agent so that we invest our energy in developing the drugs that have the most potential." Drug candidates that are validated early can be developed and brought to preclinical and clinical trials. "If we can find even small populations of patients who will benefit from a drug, we will bring it forward. Of course, we want to help as many patients as we can, but we

[Continued on **page 6**]

Compass

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

Advanced Renal Cell Carcinoma

Surgery and/or systemic therapy can help manage disease

By Sunni Hosemann

Introduction

This discussion addresses renal cell carcinoma (RCC) with one or more distant metastases. Rarer renal cancers such as renal sarcoma and Wilms tumor are not considered here.

RCC, which accounts for 85%–90% of renal cancers, has five histologic types. Clear cell histology, often called conventional RCC, is seen in 80%–85% of RCCs. Papillary cell RCC accounts for another 10%–15% of RCCs, and the remainder are chromophobe RCC, collecting duct RCC, or unclassified RCC.

Our discussion includes those RCCs in which the patient presents with a primary kidney tumor and one or more distant metastases and those in which the patient has had a previous nephrectomy and now presents with metastases. In either case, the metastases may occur at one site or be multifocal, and there may or may not be lymph node involvement because renal cancers often spread hematologically to distant sites before involving lymph nodes. The most common sites for distant metastases from RCC are the lungs and mediastinum, bones, liver, lymph nodes, adrenal glands, and brain, but metastases may involve any organ.

RCC is amenable to curative surgery if discovered at an early stage, but unfortunately, a large percentage of patients will require treatment for advanced disease. According to Eric Jonasch, M.D., an associate professor in the Department of Genitourinary Medical Oncology at The University of Texas MD Anderson Cancer Center, 25%–33% of RCC patients present with metastatic disease, and 20%–40% of patients who undergo treatment for localized disease will develop metastases later. "In short, this means that approximately half of patients with RCC will require treatment for metastatic disease," he said.

The high incidence of metastatic disease suggests a need for effective systemic therapies for the initial treatment of patients who have advanced disease and for adjuvant use in those with lower stage disease who are at risk of progression. However, until recently, few useful systemic agents had been identified.

Because RCC has proven particularly unresponsive to traditional (cytotoxic) chemotherapy agents, these are not used in the treatment of RCC with one exception: patients whose tumors have sarcomatoid features are treated with gemitabine and doxorubicin or with other agents that have activity against sarcoma. Any of the histologic subtypes of RCC may exhibit a component of sarcomatoid differentiation, which is thought to be a high-grade transformation that portends a more aggressive course of disease.

For most RCC subtypes, few options were available for the treatment of metastatic disease or for patients at high risk of developing metastases until cytokine immunotherapies, notably interleukin-2 (IL-2) and interferon alfa, emerged in the 1990s. High-dose regimens of IL-2 were found to produce complete remissions in 6%–8% of patients with metastatic RCC and a cure in 5%. However, high-dose IL-2 is highly toxic and thus appropriate only for the subset of patients who can tolerate it and are likely to benefit from it: those with clear cell histology, good performance status, and a small metastatic burden. Furthermore, the regimen requires hospitalization and should be administered only in a center with specialized supportive care.

Interferon alfa produces more modest benefits but has a lower toxicity profile and is easier to administer than IL-2. Thus, interferon alfa has been used in more patients and more research protocols than has IL-2. Because interferon alfa has not demonstrated a survival benefit over other agents, it is not currently used as a first-line, single-agent therapy but is used in combination with newer targeted agents.

A new era in the treatment of metastatic RCC commenced around 2005, when targeted agents with activity against RCC began to appear. Since that time, the median survival for patients with metastatic RCC has increased from 10 months to more than 20 months. The development of these agents grew out of an increased understanding of RCC pathogenesis at the molecular level, in particular from the study of the von Hippel–Lindau tumor suppressor gene *(VHL)*. A challenge for using these agents is deciding which one to give to a particular patient and how best to deploy them along with surgical interventions.

Seven targeted agents have been approved by the U.S. Food and Drug Administration for use in metastatic RCC. Sunitinib, sorafenib, pazopanib, axitinib, and bevacizumab are antiangiogenic agents targeting the vascular endothelial growth factor (VEGF) pathway, and temsirolimus and everolimus are mammalian target of rapamycin (mTOR) in-

[Continued from **page 3**]

CONTRIBUTING FACULTY, THI

Eric Jonasch, M.D.
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hibitors. "Whereas conventional cytotoxic chemotherapy targets the tumor cells, the anti–VEGF agents target the microenvironment—the milieu in which they grow," said Nizar M. Tannir, M.D., an associate professor in and deputy chair of the Department of Genitourinary Medical Oncology.

The targeted agents are easier to administer (many are oral agents) and have fewer side effects than traditional immunotherapies. According to Surena F. Matin, M.D., an associate professor in the Department of Urology, the advent of these new agents has changed the paradigm for the treatment of advanced kidney cancers. "The old approach was to remove the kidney first, even in patients with metastatic disease," he said, "but the new classes of medicines available today are changing that, and we have more options."

Treatment options

The standard treatment options for patients who present with metastatic RCC are nephrectomy and metastasectomy, cytoreductive surgery followed by systemic therapy, or first-line systemic therapy.

The approach for an individual patient is best determined by a multidisciplinary team in which medical and surgical oncologists collaborate to weigh the many factors to be considered.

Surgery

Among the first tasks in weighing a patient's treatment options are to assess whether the disease is resectable and to determine the patient's ability to tolerate surgery. Resectability depends largely on the location and distribution of primary and metastatic disease. Dr. Matin said that surgery to excise disease (nephrectomy and metastasectomy) is a reasonable consideration for a patient whose disease is primarily in the kidney with a small metastatic burden—perhaps a solitary metastatic lesion—or for a patient who presents with a solitary metastasis after a previous nephrectomy. Conversely, a patient with a small primary tumor and a larger metastatic burden—perhaps multifocal metastases—is less likely to benefit from surgery.

Additional considerations can help identify patients who will benefit from surgery and spare others from an ineffectual operation. The following risk factors—which were identified in a study led by Christopher Wood, M.D., a professor in and deputy chair of the Department of Urology—indicate that surgery is not likely to help, as survival outcomes are about the same for patients with more than three of these factors regardless of whether the patients do or do not undergo surgery:

- symptoms from metastases,
- elevated lactate dehydrogenase (LDH) levels,
- metastases in the liver,
- retroperitoneal lymph node involvement,
- supradiaphragmatic lymph node involvement, or
- a locally advanced primary tumor.

For some patients, nephrectomy may be indicated to alleviate symptoms, notably pain and hematuria.

Patients with potentially resectable primary tumors and multifocal resectable metastases may benefit from cytoreductive surgery followed by systemic therapy. Cytoreductive surgery became part of the therapeutic regimen for metastatic renal cancers with the advent of immunotherapies in the early 1990s.

According to Dr. Wood, the cytoreductive surgery involves the removal of as much tumor-bearing tissue as possible, including that at the primary site, lymph nodes, and metastases.

Studies of cytoreductive surgery followed by immunotherapy showed that while not all patients benefited, some had a clear survival benefit, and criteria to select candidates for this treatment emerged. These criteria are good performance status; the presence of clear cell histology; the absence of brain, liver, or bone metastases; and the absence of sarcomatoid features.

Postoperative systemic therapy

Despite the advent of targeted agents, high-dose IL-2 therapy (preceded by cytoreductive surgery) remains the only known cure for metastatic RCC. Because of the rigor and toxicity of this treatment course, however, it must be used judiciously in carefully selected patients. Although only a small percentage of patients will be able to receive this treatment, it is important to identify potential candidates before any other agents are administered because studies indicate that the benefit is less and the toxicity may be higher for patients who have received targeted therapies prior to IL-2 than for those who have not. The selection criteria for IL-2 treatment are a good performance status without significant comorbidities, clear cell histology, and adequate risk scores.

The two risk scoring systems most often used by clinicians to direct RCC therapy are the Memorial Sloan-Kettering Cancer Center (MSKCC) and the University of California Los Angeles Survival after Nephrectomy and Immunotherapy scales. The widely used MSKCC risk score takes into account the patient's performance status, the length of time from initial diagnosis of RCC to initiation of therapy, and serum LDH, hemoglobin, and calcium levels to stratify patients as having favorable, intermediate, or poor risk. In addition to these factors, the patient's attitude toward risk must be addressed and taken into account when high-dose IL-2 therapy is considered.

For patients who are not candidates for high-dose IL-2 therapy, postoperative systemic therapy options include the newer targeted agents.

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Christopher G. Wood, M.D.
Professor and Deputy Department Chair, Urology

CELL CARCINOMA: Treatment Options

Variables Considered for Each Patient

- Performance status
- Primary tumor removed?
- Resectability of primary tumor and metastases
- Tumor histology
- Location/distribution of disease
- Symptoms
- Risk criteria

Outcome-Based, Initial Treatment Options

Nephrectomy and metastasectomy

OR

Cytoreductive nephrectomy before systemic therapy

OR

Systemic therapy

OR

Clinical trial or observation

Dr. Jonasch said that bevacizumab is used in tandem with interferon alfa, but sunitinib, sorafenib, pazopanib, axitinib, temsirolimus, and everolimus are currently used singly and sequentially rather than in combination. Although the idea of using combinations that target more than one pathway or different parts of a single pathway is logical, early phase I and II trials indicated that the drugs' toxicities tend to be additive, even when drugs with differing toxicity profiles are used.

"Although the ultimate goal of these agents is to be able to target the molecular profile of each individual tumor and thus truly personalize treatment, we are not at that point yet," Dr. Tannir said. Thus, for now, the choice of which agents to use and how to sequence them is decided on the basis of tumor histology and the prognostic risk scores described above.

In general, the antiangiogenic agents appear to be most helpful for patients in the favorable and intermediate risk groups, and the mTOR inhibitors have been shown to benefit patients in the poor risk category. However, the effectiveness of combining cytoreductive surgery with newer targeted agents in the same manner as IL-2 has yet to be determined in clinical trials.

First-line systemic therapy

Agents recommended for first-line treatment of metastatic RCCs with predominantly clear cell histologies include sunitinib, sorafenib, pazopanib, bevacizumab, and temsirolimus. As clear cell histologies are the most common, more data about them are available from studies than for the rarer non–clear cell types. Although some data support the use of sunitinib, sorafenib, temsirolimus, and erlotinib in the treatment of non–clear cell RCC, patients with these histologies are currently best served in clinical trials of experimental agents.

Systemic therapy is indicated as an initial treatment for patients who do not meet the criteria outlined above for nephrectomy/metastasectomy or cytoreductive surgery followed by systemic therapy. The group not meeting the criteria for surgery includes patients who present with a large metastatic burden or other characteristics that place them in the poor risk group—a category of patients for whom there were no effective therapies prior to the development of targeted agents.

In some patients, initial systemic therapy can shrink a large primary tumor and render it amenable to surgery. Reducing disease burden can also enhance fitness for surgery in some patients.

Other patients considered for first-line systemic treatment at MD Anderson are those who have the risk factors listed above that indicate they would be unlikely to benefit from surgery. "In these instances, systemic therapy can provide a therapeutically rich period of observation," Dr. Jonasch said.

Dr. Tannir explained that giving targeted therapy before nephrectomy can help determine whether a patient is likely to benefit from surgery. After receiving systemic therapy, as many as 20% of such patients will have progressive disease. These patients would not benefit from surgery and can thus be spared its morbidity. Patients without progressive disease usually undergo cytoreductive nephrectomy at a time determined to be optimal for each patient or, in patients treated in clinical trials, after a fixed number of cycles of a particular agent. "Systemic therapy is a way of letting the disease declare itself," he said. MD Anderson pioneered this approach, which has an additional benefit: "We can interrogate the tissue eventually removed in surgery to analyze key pathways and targets and compare them to untreated tissue from nephrectomy and metastasectomy specimens," he said. This information can be used to guide future research and therapy.

Many patients respond to first-line treatment with targeted agents, and their disease stabilizes. But these agents have not proven curative, and most patients treated with them will eventually experience disease progression. "We need to understand more about what determines response and disease progression," Dr. Tannir said. "What happens in the tumor and its microenvironment that causes the drug to cease being effective?"

Some patients can enjoy years of partial or near-complete remission but over time develop other health issues related to cumulative toxicities of therapy. The most common of these issues are nephrotic syndrome and hypertension. "We need to better understand the mechanisms involved," Dr. Tannir said, noting that some of the effects are not simply side effects but may actually be markers of response to the drugs. "We need a concerted effort to work with specialists in nephrology, cardiology, pulmonology, and endocrinology to better understand these complications and how to manage them."

Observation

Although observation (without treatment) is not listed among the standard alternatives for managing RCC, Dr.

[Continued from **page 5**]

Tannir said that this is the wisest initial course for a minority of patients because the disease must be assessed in the context of a patient's overall health, comorbidities, and life expectancy. "This is part of the art of medicine that cannot be listed in templates or guidelines," he said. For example, patients who present after a previous nephrectomy with small and asymptomatic metastases in the pancreas, lymph nodes, or lungs may have indolent disease, particularly if an extended period has elapsed since initial treatment. For such patients—particularly if they are elderly or have significant comorbidities—the RCC is less likely to shorten life compared with the comorbid illnesses. For these patients, treatment may pose unnecessary risk or negatively impact quality of life and may reasonably be deferred until their disease progresses.

On the horizon

Although recent advances in understanding RCC have resulted in agents that target the disease at the molecular level, it is not yet possible to match specific agents to individual histologies in a truly customized way.

Ongoing studies continue working toward the goal of individualized therapy. One of the most important initiatives at MD Anderson is the Sequential Two-Agent Assessment in Renal Cell Carcinoma Therapy (START) trial. Dr. Tannir is the principal investigator of the study, in which patients with metastatic clear cell RCC and a prior nephrectomy are randomly assigned to receive one of six two-agent sequences of everolimus, bevacizumab, or pazopanib, receiving one of these three agents up front and a different one when disease progression is noted. An important part of this trial is the collection of tissue and blood samples along with functional imaging studies to observe response and disease progression. "We will learn about the characteristics of patients who respond and their profile when the disease progresses," Dr. Tannir said.

Dr. Tannir pointed out that in the excitement over targeted agents, less attention has been focused on immunotherapies. But two newly identified immune pathways (PD1 and CTLA4) and agents that target them have rekindled interest in immunotherapies.

Finally, although von Hippel–Lindau disease is rare, the study of RCC associated with the hereditary disease will play a pivotal role in determining the best sequence of newer agents. Dr. Jonasch explained that many of the nonhereditary RCCs have a *VHL* mutation that exists only in the tumor. In patients with von Hippel–Lindau disease, however, the mutation can be seen in other cells, such as white blood cells, which are more amenable to study. Dr. Jonasch said the study of *VHL* mutations and the agents that act on their pathways could lead to better treatments for all patients and help determine the best sequence of treatment for each individual. Stressing the importance of finding effective first-line treatments, he said, "You don't have an infinite number of times to intervene with kidney cancer." ■

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Gene Mapping Technology and Drug Development

[Continued from **page 2**]

are not driven by how many vials of a drug we can sell."

Not only do the institute's research teams coordinate with each other, they also work closely with other researchers and clinicians at MD Anderson. For example, Dr. Draetta regularly consults physicians in the Department of Investigational Cancer Therapeutics to determine what drugs currently in clinical trials are likely to become the standard of care that might be given along with a drug he is developing for a particular type of cancer.

Dr. Draetta sees this ability to bring together all aspects of research as a unique advantage of the institute's location at a major cancer center. "I worked in the pharmaceutical industry for many years. My teams identified many compounds and developed them on our own, but we missed the ability to go back and open a dialogue with the biologists who did the initial research," Dr. Draetta said. "Now, we are engaging biologists and clinicians early on."

Genomic information can also identify which patients are most likely to benefit from a drug. "We're seeing in clinical trials that if you match the therapy with the mutation, you get much better results," Dr. Draetta said, adding that matching therapy to mutations also can spare patients from unnecessary treatment.

"I'm very enthusiastic about this new research model," Dr. Draetta said. "We want to use bioinformatics—computational tools—to look at common points of attack. It's about working together and coordinating the effort." ■

FOR MORE INFORMATION

Dr. Giulio Draetta 713-792-6803

Do Nutritional Supplements Help Prevent Cancer?

For many people, the risks may outweigh the benefits

HOUSE•CALL PATIENT INFORMATION SHEET

Forty-five percent of American men and 55% of American women take nutritional supplements to prevent cancer and other serious health conditions. While some supplements have proven to be effective treatments for some medical conditions, the benefits of others are not scientifically proven, and a few have actually been proven dangerous when taken in excess.

The U.S. Food and Drug Administration (FDA) categorizes nutritional supplements under the general umbrella of foods rather than drugs. Unlike drugs, which cannot be marketed until they have passed clinical trials and a rigorous approval process, foods and nutritional supplements cannot be removed from the market by the FDA unless they are proven to be dangerous or have false label information. Although supplement manufacturers are required to list all active ingredients on their products' labels and follow FDA manufacturing guidelines, the supplements do not have to be proven safe or effective.

Possible dangers

Because Americans tend to get enough of most vitamins in their normal diet, taking extra vitamins can cause an overdose; in 2008, more than 69,000 cases of toxicity due to a vitamin overdose were reported.

For example, taking more than 7.5 mg/day of vitamin A can lead to headaches, irritability, anoxia (lack of oxygen to the tissues), dry or cracked skin, and osteoporosis (reduced bone density). This harmful dose is available over the counter in many stores.

Another danger of supplements is that some can interact with some medicines in ways that harm the patient. People taking prescription medications should inform their health care team about any nutritional supplements they are taking.

In some studies, certain vitamins have also been associated with promoting cancer. One trial of selenium for the prevention of prostate, lung, or colon cancer recurrence was stopped because men who took 200 µg of selenium per day (12 times the recommended dose) had a higher recurrence rate than patients who did not take the supplement.

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The vitamin D debate

Vitamin D and its effects on cancer have recently received a lot of attention in the media, but scientists have not reached a consensus about the effectiveness of vitamin D supplements for preventing cancer.

In a study currently under way, thousands of healthy men and women who take vitamin D and/or fish oil supplements will be examined at regular intervals for 5 years to determine the benefits of these supplements for preventing cancer and cardiovascular disease. Secondary goals of the study are to observe whether the supplements affect cognitive problems, diabetes, hypertension (high blood pressure), autoimmune disorders, bone fractures, mood disorders, or infections.

Nutrients in foods

An apple a day may really keep the doctor away. Fruits and vegetables contain important nutrients and fiber, which helps protect against colon cancer.

Studies have shown that eating fresh fruits and vegetables also reduces both the risk and recurrence rate of breast cancer. For example, women with *BRCA1* gene mutations have a lifetime breast cancer risk around 60%, but one study found that the risk dropped to less than 30% when these women included a large variety of produce in their regular diet.

Another study showed that women who regularly ate mushrooms had a breast cancer risk about two-thirds lower than those who did not, and those whose daily diet included both mushrooms and green tea had an even lower breast cancer risk.

In 2010, the American Institute for Cancer Research estimated that a third of the cancers that occur every year in the United States could be prevented by lifestyle changes, including eating more whole foods.

The reason whole foods are more beneficial than vitamin supplements is probably that whole foods contain many nutrients that work synergistically to protect against cancer. Salmon, for example, is superior to salmon oil supplements because although both provide fatty acids, salmon provides nutrients not found in oils, such as vitamins D and B, amino acids, calcium, and selenium.

Foods known or believed to help prevent cancer include:

- all berries
- grapes
- tomatoes
- mushrooms
- green tea
- salmon
- squash
- broccoli
- cauliflower
- cabbage
- brussels sprouts
- linseed
- flaxseed

Physicians sometimes prescribe supplements to treat certain medical conditions, but for most people, a diet that includes healthful foods can eliminate the need for supplements. Bon appétit! ■

– J. Delsigne

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IN BRIEF

Drug Provides Symptom Reduction and Survival Advantages for Myelofibrosis Patients

Ruxolitinib, which has been shown to alleviate debilitating symptoms and reduce the size of swollen spleens in patients with myelofibrosis, in November became the first drug to be approved by the U.S. Food and Drug Administration for the treatment of that disease.

About 3,000 new cases of myelofibrosis are diagnosed in the United States each year. Myelofibrosis is caused by an accumulation of abnormal bone marrow cells that triggers an inflammatory response, scarring the bone marrow and limiting its ability to produce blood. As the body tries to compensate for the lack of red blood cells produced by the bone marrow, the spleen doubles or even triples in size in about 80% of patients.

Patients with myelofibrosis have shortened survival due to progressive disease or transformation to acute leukemia. Srdan Verstovsek, M.D., Ph.D., an associate professor in the Department of Leukemia at The University of Texas MD Anderson Cancer Center, said, "Most of these patients die from body wasting, organ failure, and other disease complications within 5–7 years."

About half of myelofibrosis patients have a mutated *JAK2* gene. This gene is responsible for normal blood cell production, and the mutation causes aberrant blood cell production by the bone marrow. In patients without a mutation in *JAK2*, its abnormal function has other causes. Ruxolitinib targets the JAK2 enzyme regardless of whether the gene is mutated and so can treat patients with or without *JAK2* mutations. All patients with myelofibrosis have the same chance to benefit from ruxolitinib.

In a phase III clinical trial at MD Anderson and other institutions, myelofibrosis patients treated with ruxolitinib not only had reduced symptoms but also had a higher survival rate than did those receiving a placebo. At a median follow-up of 51 weeks, the mortality rate was 8.4% among patients receiving ruxolitinib compared with 15.6% among patients receiving a placebo.

"The phase I/II clinical trial showed that ruxolitinib improves quality of life for many patients; this phase III study indicates that the drug may also extend survival in a patient population that has lacked effective treatments," said Dr. Verstovsek, the principal investigator for both trials.

The report of the phase III trial was published in the March 1 issue of the *New England Journal of Medicine*. ■

> **"The drug may also extend survival in a patient population that has lacked effective treatments."**
>
> **– Dr. Srdan Verstovsek**

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