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Preventing and Treating Graft-Versus-Host Disease After Stem Cell Transplantation

By Kathryn L. Hale

Each year, thousands of patients with hematologic malignancies undergo allogeneic (donor) stem cell transplantation (SCT), which offers a chance at cure. Graft-versus-host disease (GVHD) is a potentially deadly complication of this therapy and occurs in 25%–60% of patients. However, clinicians and researchers are continually working to reduce the rate of GVHD occurrence and improve patient outcomes.

SCT is typically given to patients with a hematologic malignancy such as lymphoma, leukemia, or myeloma after they receive a relatively high dose of chemotherapy or radiation therapy, referred to as the conditioning regimen. The goals of the conditioning regimen are to eradicate the underlying malignancy and to suppress the patient's immune system so that the donor stem cells are accepted. These treatments—and in some cases, the cancer itself—damage the bone marrow and thus disable the immune system. By reconstituting the stem cells in the bone marrow, SCT restores the patient's ability to mount an immune response to pathogens. The restored immune system also recognizes and reacts to cancer cells to prevent disease recurrence.

Chronic graft-versus-host disease following allogeneic stem cell transplantation may resemble various autoimmune conditions. The patient above exhibits symptoms of scleroderma: thickening of the skin on the hands with fascial involvement.

Although allogeneic SCT offers great promise through the development of this "graft-versus-cancer" effect in the transplant recipient, it is not without risks and complications. The most common—and potentially serious—of these is the graft-versus-host (GVH) effect, in which the restored immune system targets the patient's healthy tissues. This can create the potentially life-threatening complication known as GVHD.

GVHD risk factors

Amin Alousi, M.D., an associate professor in the Department of Stem Cell Transplantation and Cellular Therapy at The University of Texas MD Anderson Cancer Center,

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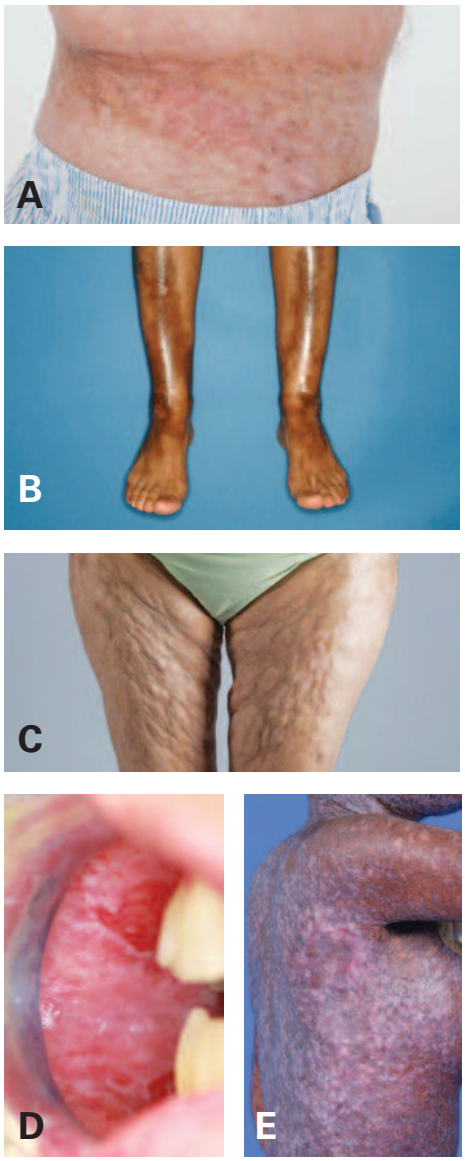
oversees clinical research related to the prevention and management of GVHD. "An individual patient's risk of developing GVHD depends on the presence of a number of risk factors," he said. "While many risk factors are inherent to the patient and the cancer, the single biggest factor is the donor."

Donors are selected by human leukocyte antigen (HLA) typing. Historically, siblings were the most common donor source. A sibling, having the same parents as the patient, has a 25% chance of being an exact match.

"Allogeneic SCT from an HLA-matched sibling donor carries the lowest risk of GVHD," Dr. Alousi said. "Unfortunately, a matched sibling donor often is not available, and we have to turn to alternative donors." Because family sizes are decreasing in the United States, matched unrelated donors are currently the most common donor source. When a patient lacks a suitable HLA-matched sibling, a search is initiated in the worldwide volunteer donor registry, which lists more than 16 million potential donors. An HLA-matched donor is identified from this registry 30%–50% of the time.

When a matched donor cannot be found in the registry, the transplant team looks at other alternatives: a half-matched family member such as a parent, son or daughter, or haploidentical sibling; an unrelated donor who is not an exact match; or an umbilical cord stem cell transplant, which does not require an exact match. "But when we do that," Dr. Alousi said, "the risk of GVHD increases. The less matched the donor, the greater the GVHD risk. The greater the risk, the more aggressive we need to be in taking measures to prevent GVHD both during and after the transplant."

Even a perfect HLA match does not preclude the risk of GVHD, as mismatches of other proteins involved in the immune response confer some risk. Other risk factors include patient age (older patients are more likely than younger patients to develop GVHD) and sex mismatch between donor and recipient (for example, transplantation from a female donor, especially one who has been pregnant, to a male recipient carries a higher risk of GVHD).



The symptoms of chronic graft-versus-host disease vary greatly and may resemble autoimmune diseases such as scleroderma (A, B, and C) or lichen planus (D and E).

Other risk factors for GVHD arise from the patient's cancer itself. Higher cancer stage and more extensive previous therapy increase the risk of GVHD after SCT. Patients whose cancer has relapsed multiple times, has been heavily treated, or is not in remission at the time of the transplant are also at increased risk of GVHD.

Reducing GVHD risk

One approach to reducing the risk of GVHD, particularly in patients who are older or have comorbid conditions, is to give a less intensive conditioning regimen. "There's no one standard conditioning regimen," Dr. Alousi said. "Rather, we individualize the conditioning regimen to what we think the patient can tolerate. A less intensive conditioning regimen can reduce the risk of GVHD. The problem is that the less intensive regimen may also increase the risk of cancer relapse. It's a fine line we're walking."

Another approach to reducing GVHD risk is to reduce the activity of T lymphocytes—which are largely responsible for the GVH effect—by physically removing them from stem cells before transplantation. According to Dr. Alousi, this approach can reduce the risk of GVHD, but at a great price. "If we remove the T lymphocytes, they're no longer there to fight infections," he said. "It slows patients' recovery and puts them at greater risk of infection that they can't fight off."

Dr. Alousi's research focuses on finding a new strategy that strikes a balance between these two approaches: "We're looking for an approach that reduces the risk of GVHD while not reducing the graft-versus-cancer effect or the patient's capacity for fighting infections. Ideally, we want to develop strategies that target the cancer proteins without risking damage to host cells."

GVHD clinical management

GVHD takes one of two forms: acute or chronic. Acute GVHD usually occurs within the first 100 days after transplantation, whereas chronic GVHD occurs after day 100. Although the risk factors for the two are the same, the underlying mechanisms are believed to differ.

The symptoms of acute and chronic GVHD also differ. Patients with acute GVHD tend to have symptoms that include skin rashes, diarrhea, liver problems, and/or nausea and vomiting. The manifestations of chronic GVHD are notably varied. Chronic GVHD can affect any system of the body and tends to resemble diseases such as scleroderma, lupus erythematosus, and sicca syndrome. Chronic GVHD affects

25%–50% of patients who undergo allogeneic SCT.

According to Dr. Alousi, various means are used to prevent acute GVHD. These typically include an immunosuppressive regimen of one or more drugs such as tacrolimus, cyclosporine, methotrexate, and mycophenolate that begins at the time of the transplant. "As the graft matures, the host becomes more tolerant of it, and we slowly taper the immunosuppressive drugs to allow the donor cells to coexist with the host's cells," Dr. Alousi said. "However, about 20% of patients have to stay on the immunosuppressive regimen indefinitely." Most current approaches for reducing GVHD risk have been more successful in minimizing the risk for acute than for chronic GVHD. However, reducing chronic GVHD risk is an area of active research.

Since GVHD can affect multiple organ systems, its management may require coordination among dermatologists, ophthalmologists, pulmonologists, and other specialists. The management goals for acute or chronic GVHD are to 1) catch it early and stop the process, preventing the disease from worsening; 2) treat symptoms and provide supportive care, minimizing GVHD's effects on quality of life; and 3) prevent long-term toxic effects from the GVHD therapy.

The only treatment now considered standard for either acute or chronic GVHD is corticosteroids. Because long-term steroid use is linked to many potentially severe toxic effects, including diabetes, increased infection risk, profound muscle weakness, and cancer recurrence, development of alternative therapies is a priority for GVHD specialists.

Current clinical trials for GVHD treatment are investigating combinations of a steroid such as prednisone with other immunosuppressive drugs that will allow lower doses and earlier tapering of the steroid. Some regimens incorporate a technique known as extracorporeal photopheresis to reduce the GVH effect. The patient's blood is circulated through a device that removes the white blood cells and platelets, treats them with a chemical that is then activated by exposure to ultraviolet light, and returns them to the circulation.

Community physicians key to identifying chronic GVHD

At MD Anderson and most SCT centers in the United States, patients stay in the hospital following SCT until recovering blood cell counts give clear evidence of engraftment, typically about 4 weeks. The patients are then discharged from the hospital and monitored closely by the transplant team until roughly 100 days after the transplant to make sure that their immune system is recovering, that they are not developing infection, and—most important—that they are not developing GVHD. Around day 100, the SCT patients are transitioned to the care of a physician in their home community.

The transplant team at MD Anderson works closely with the community physician. The Stem Cell Transplant Survivorship Clinic, which Dr. Alousi oversees, provides all the needed information to the community physician, who is given tools to help screen for chronic GVHD and information about what to do if GVHD is suspected. The physician can reach the survivorship clinic's medical staff at any time with questions or concerns.

"We ask the community physician to be our 'eyes and ears' with the patient," Dr. Alousi said. "Chronic GVHD is a clinical diagnosis. It can't be detected with blood tests or imaging studies. The clinical signs may be very subtle." The more common symptoms of chronic GVHD include skin rash, dry eyes, mucosal membrane dryness or pain, and joint stiffness. The less common symptoms include jaundice and lung or digestive problems. However, according to Dr. Alousi, chronic GVHD can look like "a hundred different syndromes."

Quality of life after SCT

Studies have shown that the strongest predictor of long-term quality of life after SCT is the presence or absence of chronic GVHD. Transplant recipients who do not get chronic GVHD tend to have a quality of life similar to other people their age. While chronic GVHD can have a deleterious effect on quality of life, recipients whose chronic GVHD can be controlled tend to have a quality of life similar to those who do not get chronic GVHD. "GVHD and survivorship are very integrated," Dr. Alousi said. "Helping patients live well after transplantation is in essence preventing or controlling GVHD. My role as a GVHD specialist is also a role in survivorship, in helping patients have the best possible quality of life after the transplant."

Future research directions

An emerging area of research is the identification of biomarkers for GVHD. An effective biomarker might be able to predict which patients are likely to get GVHD after SCT, which patients who get GVHD are likely to have a more severe case that requires more aggressive therapy, or which patients with acute GVHD are most likely to develop chronic GVHD. An international effort is now under way to find such biomarkers and develop them for clinical use. Some progress has been made in early studies: researchers now know of some blood proteins that might indicate early—before the appearance of symptoms—which patients are developing GVHD. Additional markers are being studied to identify patients who are less likely to respond to standard initial GVHD therapy.

"We haven't come far enough yet to put these markers to use in the clinic," Dr. Alousi said. "And a biomarker is worthwhile only if there's an effective therapeutic approach to act on it. Right now we're trying to perfect the biomarkers so we can develop the therapies that specifically target them." Nevertheless, Dr. Alousi said he and his colleagues are optimistic. "We've developed several promising strategies, and we're going to keep at it until we find the ones that work." ■

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

Breast Cancer Risk Reduction

Women at increased risk have multiple options

By Sunni Hosemann

Introduction

Various interventions and strategies can reduce a woman's chances of developing breast cancer. Some of these strategies—dietary and lifestyle changes, for example—come with the difficulty and inconvenience of change but do not pose additional disadvantages or health risks. At the other end of the spectrum, risk-reducing surgeries—bilateral mastectomy and salpingo-oophorectomy—have inherent risks. Before discussing these options with a woman, a physician must first conduct an accurate, personalized risk assessment.

This discussion addresses strategies for reducing the risk of breast cancer in women. Although men also can develop breast cancers, these cancers are rare, and the same risk models and risk-reduction strategies do not apply.

Risk

Cancer risk is an estimate of the chance of developing a particular type of cancer over the course of a lifetime for members of a particular group. According to the American Cancer Society, a woman in the United States has a 1 in 8 chance of developing breast cancer at some time in her life.

While such estimates reflect how widespread the disease is in a population, they are not particularly helpful for determining the cancer risk for a given individual. In the area of breast cancer prevention, current efforts are aimed at identifying individual women's short-term risks of developing the disease. The main risk factors considered in such assessments are age, family history, personal history of premalignant breast lesions (such as ductal or lobular atypical hyperplasia or carcinoma in situ), menstrual and childbearing history, previous radiation therapy, breast density, and genetic mutations.

Risk assessment

According to Therese Bevers, M.D., a professor in the Department of Clinical Cancer Prevention and medical director of the Cancer Prevention Center at The University of Texas MD Anderson Cancer Center, various tools are available to assess breast cancer risk. The modified Gail model is a standard and commonly used tool developed by the U.S. National Cancer Institute. Others in regular use are the Claus and Tyrer-Cuzick models. None of these tools applies to all women, and each represents one part of an overall risk assessment.

The tools most commonly used to assess whether a woman is a candidate for genetic testing are the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm and the BRCAPRO model.

Genetic risk

Five to ten percent of breast cancers are hereditary, and women who have a strong family history of breast cancer have a significantly increased risk of developing the disease.

BRCA1 and *BRCA2* gene mutations are linked specifically to hereditary breast and ovarian cancers. Women with a *BRCA1* or *BRCA2* mutation have a 50%–60% lifetime risk of developing breast cancer. Also associated with higher breast cancer risk are mutations in the *TP53*, *PTEN*, *CDH1*, *ATM*, *CHEK2*, *CDH1*, and *STK11* genes, which are linked to hereditary cancer syndromes such as Li-Fraumeni, Cowden, hereditary diffuse gastric cancer, and Peutz-Jaegers syndromes. Mutations in these and the *BRCA* genes are considered high-penetrance mutations, meaning that a high proportion of individuals with the genotype develop breast cancer.

The family history characteristics that should raise suspicion of identifiable genetic mutations and prompt further investigation include having at least one first-degree relative who was diagnosed with breast cancer at a young age (<40 years), having more than one close relative with breast or ovarian cancer, having a first-degree relative diagnosed with breast and ovarian cancer or bilateral breast cancer, having a male relative with breast cancer, or being of Ashkenazi Jewish descent.

Genetic counseling and testing

According to Banu Arun, M.D., a professor in the Department of Breast Medical Oncology and co-chair of the Clinical Cancer Genetics Program, genetic testing is not a general screening tool and should be considered only when a relevant mutation is strongly suspected. Genetic testing is expensive and, if not undertaken carefully, may produce results that are not useful. For example, she said, there are

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more than 2,000 variants of *BRCA* mutations, and no single test identifies them all. "It is crucial to use the right test and to test the right person," Dr. Arun said.

When one or more family members are concerned about hereditary cancer, testing should begin on the cancer patient to identify a specific mutation to target for any additional testing of unaffected relatives thought to be at high risk. If a relative with cancer cannot be tested, then —in addition to clinical judgment—risk-assessment models that calculate the risk of carrying a *BRCA* mutation can be used to help determine whether a healthy woman should undergo genetic testing.

Dr. Arun stressed the importance of meeting with women before they undergo genetic testing to discuss the possible test results and their implications and meeting with women after genetic testing to discuss the actual test results. A negative result is considered uninformative; it may be a false negative result, and it does not eliminate the possibility that the woman has gene mutations other than the ones tested for. A positive result verifies that the person has a mutation and therefore is at increased risk, but it does not predict whether the person will actually develop cancer. For these reasons, it is important to carefully select candidates for genetic testing, to select the appropriate test, and to ensure that genetic counseling precedes and follows testing.

Options for Breast Cancer Surveillance and Risk Reduction

RISK:	*Variables Considered for Each Patient*	*Outcome-Based, Standard Options*
Average	• Age	**Screening every 1–3 years** (guidelines vary)
Increased	• Genetic status • Family history • Personal medical history • Age • Menopausal status • Comorbid conditions • Risk tolerance • Personal preference	**Lifestyle modifications** + **Increased surveillance** +/– **Chemoprevention** • Tamoxifen • Raloxifene • Exemestane • Clinical trial OR **Prophylactic surgery** • Bilateral mastectomy AND/OR • Bilateral salpingo-oophorectomy

Risk reduction

According to Powel Brown, M.D., Ph.D., chair of the Department of Clinical Cancer Prevention, the current strategies for managing breast cancer risk consist of enhanced surveillance, lifestyle modifications, chemoprevention, and prophylactic surgery. The benefits and associated risks or side effects of these options vary. A woman's preferences, risk tolerance, and attitudes toward cancer and medical interventions all play important roles in her choice of strategy.

Increased surveillance and lifestyle modifications

Recommendations on screening and surveillance for women at all levels of breast cancer risk are available through the National Comprehensive Cancer Network, the American Cancer Society, the U.S. Preventive Services Task Force, and other sources. Recommendations for women who have a high risk of breast cancer include undergoing breast examination and mammography (plus magnetic resonance imaging in some cases) more frequently or at earlier ages than recommended for women at average risk.

According to Dr. Brown, women who have a *BRCA* mutation should also undergo transvaginal ultrasonography and laboratory tests for cancer antigen 125 levels to screen for ovarian cancers. Such women should also be monitored

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by a gynecologist who is familiar with hereditary breast and ovarian cancers.

Dr. Brown said that counseling for women at any risk level should include a discussion of the benefits of diet, physical exercise, and weight control and the increased breast cancer risks associated with alcohol use and hormone replacement therapy. These factors are not trivial—the National Cancer Institute estimates that regular physical exercise alone can lower breast cancer risk by 20%–40%.

Risk-reducing surgery

Risk-reducing surgery usually is considered only for women at very high risk of breast cancer, particularly women with a *BRCA* mutation. Women with *BRCA1* mutations are more likely to have triple-negative breast cancer than those with *BRCA2* mutations.

Retrospective studies have found that bilateral salpingo-oophorectomy reduces the risk of ovarian cancer associated with *BRCA* mutations by as much as 80% and the risk of breast cancer by approximately 50% in women younger than 50 years. Salpingo-oophorectomy should be performed by a gynecologic or surgical oncologist. The surgeon will perform peritoneal washings and lymph node evaluation, submitting removed tissue for intra-operative pathologic analysis. "Experience has shown that there is an 8%–12% chance of an occult ovarian cancer already being present," Dr. Brown said.

Studies have also shown that prophylactic bilateral total mastectomy reduces breast cancer risk by 90% or more. "Prophylactic bilateral mastectomy is an elective surgery, but it greatly reduces an individual's chance of developing breast cancer in the future," Dr. Brown said. "When appropriate, I support the patient's decision to have this surgery."

Risk-reducing surgery should never be undertaken without appropriate counseling. The patient must be fully aware of all her options, including surgery. According to Dr. Arun, the women most likely to choose risk-reducing surgery are those who have known *BRCA* mutations or have had a close relative who had ovarian cancer.

Chemoprevention

Tamoxifen and raloxifene are the only drugs currently approved by the U.S. Food and Drug Administration for breast cancer risk reduction. Both drugs are selective estrogen receptor modulators, but they differ in their effects on tissues and organs as well as their side effects. For breast cancer risk reduction, either drug is prescribed for 5 years. According to Dr. Bevers, data from a large clinical trial indicated that the two drugs equally reduced the risk of invasive breast cancers during the course of treatment—cutting risk approximately in half—but longer follow-up showed that the benefits of raloxifene tapered off with time while the preventive effect of tamoxifen was more durable. On the other hand, tamoxifen has more serious side effects than raloxifene. Dr. Bevers said that women with atypical hyperplasia obtain an 86% reduction in breast cancer risk with tamoxifen or raloxifene.

A third drug currently in use for breast cancer risk reduction is the aromatase inhibitor exemestane. Aromatase inhibitors have not been compared directly with tamoxifen or raloxifene in large primary cancer prevention trials and are not currently approved for this use. However, exemestane and other drugs in the same class have shown promise for the prevention of secondary cancers when given as an adjuvant treatment in women who have already had an invasive breast cancer.

Dr. Bevers said that tamoxifen, raloxifene, and exemestane each have advantages and disadvantages. "Choosing which agent to use is a matter of weighing all of the potential benefits against risks," she said. "And each woman has a unique mix of variables that can tip the scales in favor of one approach over the other."

The first deciding factor is menopausal status. While all three agents are appropriate for postmenopausal women, neither raloxifene nor exemestane has been studied in premenopausal women (and exemestane may actually increase estrogen production in women whose ovaries are still producing it). So for now, the choices for premenopausal women who wish to use a chemopreventive agent are tamoxifen or an appropriate clinical trial.

The next consideration is whether the woman is particularly susceptible to certain adverse effects or likely to benefit from other effects. For example:

- Tamoxifen carries an increased risk of endometrial cancer that is not associated with the other agents, so whether a woman has had a previous hysterectomy is a factor to consider.
- Raloxifene is approved for the treatment and prevention of osteoporosis and thus would provide additional benefit for women affected by or at risk for osteoporosis. For women with osteoporosis, it may be reasonable to continue raloxifene beyond the 5 years recommended for breast cancer risk reduction.
- Both tamoxifen and raloxifene carry the risk of thrombotic vascular events (including stroke, pulmonary embolism, and deep vein thrombosis) and therefore are contraindicated in women who have a history of thrombosis. Exemestane does not carry these risks and thus is a better choice for such women and possibly for those who have other risk factors for thrombotic events (e.g., smoking, diabetes, atrial fibrillation, or cardiovascular disease).
- Exemestane has been associated with bone loss and so is not appropriate for women who have or are at risk of osteoporosis.

According to Dr. Bevers, women with proliferative breast lesions are the most likely to opt for chemoprevention. As with risk-reducing surgery, chemoprevention is an elective treatment, so considerable discussion and counseling are necessary to help patients make decisions. "We are developing

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Benefits of In-Person Support Groups

Face-to-face contact helps people cope with chronic illness

Support groups help people connect with others going through similar health situations. Support groups also serve as discussion forums for people with chronic illnesses as well as their family members or other caregivers. Sharing experiences with people who have a common illness often helps relieve the emotional stress associated with a chronic disease.

Unlike online or telephone support groups, in-person support groups allow members to communicate with more than just words. Stephen Collazo, a social work counselor in the Department of Social Work at The University of Texas MD Anderson Cancer Center, said he often sees support group members express sympathy with a look, nod, or furrow of the brow. "And that's different from just typing, 'I feel sorry for you,'" he said.

Face-to-face meetings can help group members develop personal connections that are more difficult to establish in online groups, according to Marisa Mir, a program coordinator with the Anderson Network, which is a program of the Department of Volunteer Services. "Some people need visual responses more than others," she said. "They want to see other people and be able to connect with them."

A typical in-person support group session can have about 10 people and lasts an hour. Most support groups are led by a social worker, counselor, or other health care professional who guides the group through a discussion. Social workers are trained to help group members process ideas or emotions together so that the members benefit from each other's experiences.

Types of support groups

The two most common types of in-person support groups are open and closed groups. Open support groups are not limited to a predetermined number of sessions, and people are not required to register beforehand. Discussion topics in open support groups usually are decided by the group members. The group leader then asks open-ended questions and guides the discussion to help the members overcome whatever emotional or coping issues they have. Many patients attend open group sessions to listen to other people's experiences or to share their own. "It's very therapeutic and beneficial for them," Mr. Collazo said. "There's a lot of value to patients' being able to tell their story and then hear other group members say, 'We understand what you are going through, and we get it. You are not alone in this, and you are not weird for having these thoughts.'"

Unlike an open support group, a closed support group can be restricted by the number of sessions or when members can join the group. Moreover, closed support groups usually require people wanting to attend the sessions to register with the group leader. Most closed support groups are highly structured, and social workers often can provide focused clinical counseling to the group members.

Some open support groups are focused on educating group members about their illnesses and concerns. In such groups, a speaker (usually a doctor, nurse, or other health care professional) is brought in to talk about some aspect of the illness in the first half of the session, and the group leader guides a discussion about the topic in the second half.

Some support groups are for patients' families rather than the patients themselves. One such group at MD Anderson is CLIMB (Children's Lives Include Moments of Bravery), a support group for children who have parents with cancer. "You see the kids come in, and they don't really know each other. You help them break down those barriers to build cohesion, and you start to work on processing questions like, 'What does it mean that my mom has cancer?'" Mr. Collazo said. "Seeing these little kids open up is fascinating. It's really interesting seeing the group transform from people who don't know each other into a supporting element for each other."

Benefits of support groups

There's more to support groups than just the "feel-good" aspect. Research has shown that people with chronic illnesses and inadequate social support have worse health outcomes than those who have adequate emotional and psychological support. Support group members can build connections and gain such support through interactions with each other.

If you are affected by a chronic illness and are looking for a support group, your physician might be able to provide information about support groups in your area. Nonprofit groups like the American Cancer Society and the American Liver Foundation also may have information about local support groups. ■

– M. *Sala*

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materials that help advance these discussions—educational videos and written materials. Some of these are already available to our patients," Dr. Bevers said.

Clearly, there is a need for chemopreventive agents that are effective but do not have toxicities. "The drugs we have at the present time have side effects that are serious enough to discourage women from taking them. Only 20% of women who are thought to be at high risk of breast cancer opt to take tamoxifen, for example," Dr. Arun said, "and we do not have agents to use to reduce the risk of developing estrogen receptor–negative breast cancers."

To that end, several studies are under way to identify agents that could reduce risk without side effects that diminish quality of life. Dr. Bevers is currently enrolling women in studies evaluating vitamin D as an agent for breast cancer risk reduction. Likewise, Dr. Arun and colleagues are enrolling patients in a phase II trial to study the risk-reducing effects of curcumin (one of the compounds in turmeric), which has anti-inflammatory properties and has been shown to exert an inhibitory effect on at least four molecular pathways that affect the proliferation of breast cancer cells in the laboratory. "Some potential risk-reducing agents are things that many of my patients like to take anyway, such as green tea and curcumin," Dr. Arun said, "but these may need to be specially formulated to increase bioavailability." A nanoparticle formulation of curcumin is being used in the phase II study.

Celecoxib, metformin, anastrozole, and lapatinib are other agents being studied for breast cancer risk reduction. Thus, women who are at high risk for breast cancer but find currently approved risk reduction strategies unacceptable may look to clinical trials for other options. ■

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