Pancreatic and Breast Cancers Linked by BRCA Gene Mutation

“A mother in her forties, who has battled and survived breast cancer, is sitting opposite me at the other side of my desk,” says John A. Chabot, MD, Chief of the Division of GI/Endocrine Surgery and Executive Director of The Pancreas Center at NewYork-Presbyterian/Columbia University Medical Center. “I am very aware that she believed, or hoped, she was in the clear after a mastectomy and a bilateral oophorectomy. Yet, I find myself discussing with her our approach to the lesion the MRI revealed on her pancreas.”

Many patients know of the association of the BRCA gene mutations with breast and ovarian cancers, and how work in this area has produced effective treatments and sometimes the means of prevention. “But very few patients,” Dr. Chabot says, “have heard that these germline mutations have been linked to several gastroenterological cancers, including pancreatic ductal adenocarcinoma [PDAC]. For men and women who carry the BRCA mutations, there is about a three- to four-fold higher risk for pancreatic cancer. Unfortunately, choices for treatment for the PDAC patient are very limited.”

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Advances in Stem Cell Transplantation (continued from page 1)

In the past, allogeneic stem cell transplantation has been limited to human leukocyte antigen (HLA)-identical sibling donors. “Generally, the perfect match would be a sibling who’s a 12 out of 12 HLA identical match,” says Adrienne A. Phillips, MD, MPH, a specialist in hematologic malignancies at NewYork-Presbyterian/Weill Cornell. “The chances of having a perfect match in a sibling is about 25 percent. So, if there is no sibling donor, and there often is not one for older patients, we would look to the unrelated donor registry.”

Adult unrelated donor transplantation was developed to meet the need to broaden the search. Recent developments of high-definition HLA typing have made the expanded use of adult matching donors more effective. Without knowing the specific identity of the HLA mismatch, determining immunogenicity was often impossible, creating associated increased risks of complications and a substantial decrease in the five-year survival rate. But remarkable precision in high-definition HLA typing has yielded increasingly defined readings of HLA types.

“We’re now able to do assessments to look at genetic information and find more degrees of patient matches,” Dr. Phillips says. “Before we were just looking at related donors, but now we can use, in addition to matched related donors, matched unrelated donors.”

Importantly, Dr. van Besien reminds us that transplantation remains a very complex procedure. “When patients come to us, we evaluate their general health and also discuss their support network because the process requires a lot of support from family and friends. We then evaluate the donor sources and that can take several weeks. We work closely with Drs. Gail Roboz and John Leonard and our other leukemia/lymphoma colleagues to see if they have alternative investigational therapies that might be considered. We don’t stand on our own. The patients benefit from their input, our input, and the collaboration between our two groups is very, very important. After we gather all this information: the donor, the health of the patient, the alternative treatments, and the social situations, it typically takes us a few weeks to come up with the treatment plan.”

The Transition to Cord Blood Stem Cell Transplantation

Still, even with better HLA-typing, there remain large numbers of patients who lack matching donors. “Greater access to potential donors for patients who do not have matching donors is being achieved with cord blood transplants – newborn donors,” says Dr. van Besien. “Umbilical cord blood contains extremely proliferative hematopoietic stem cells and a very adaptable immune system. The use of cord blood greatly reduces the risk of graft-versus-host disease and increases potent graft-versus-leukemia effects. When these pristine stem cells are transplanted into another human being, they adapt to that foreign environment without causing as many problems.”

— Dr. Koen van Besien

The cord-haplo program greatly expands the effective donor pool. “The need to find donors for those who don’t have matching siblings or matching unrelated donors, especially daunting for older patients and underrepresented minorities, can still be a major hurdle,” says Dr. van Besien. “In the last four or five years, we have been able to offer transplants to 30 to 40 percent of patients who do not have matching donors with at least a 50 percent chance of cure. The average age in our transplant program is 62. Our oldest patient is 77; our youngest is 16. There is palpable optimism.”

“Finding a half-match donor that would be supplemented by stem cells from umbilical cord blood could indeed be the answer for many patients,” says Dr. Phillips. “The registries of unrelated donors are complex. Typically we tell a patient that it takes six weeks to identify and procure a donor. One advantage of cord blood is that it’s already collected; it’s sitting in banks.”

Dr. Phillips has particular expertise in adult T-cell leukemia/lymphoma, a very aggressive type of hematologic malignancy for which transplant is the only curative option. “This is a disease where the prognosis is poor, the median overall survival is just about 10 months, and transplant is the only cure,” says Dr. Phillips. “Adult T-cell leukemia/lymphoma is caused by the HTLV virus, which disproportionately affects minorities, particularly those from the Caribbean, Asia, Africa, and Latin America. Unfortunately because of their ethnicity, it is especially difficult to find donors for these patients – matched or unmatched. Over 65 percent of minority patients do not have a donor available to them either through a sibling or from the donor registry. Working with Dr. van Besien, we have been able to increase donor options for these patients via the haplo-cord transplant program. With this program, we can find an available donor for almost anyone.”

Reasons for Optimism

Historically, the collection of stem cells for bone marrow transplants is associated with operating rooms and repeated bone marrow harvests taken directly in multiple biopsies.
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The BRCA Connection

According to Dr. Chabot, the discovery of the connection between the BRCA1 and BRCA2 mutations as a predisposing factor for PDAC grew out of a set of associations. “We started to ask the question, ‘Could people have any predisposing conditions for pancreatic cancer?’ We had already established a high-risk program focused on identifying other family members of the patient who might be at risk or have pancreatic cancer. We then wanted to see if we could determine a more complete cancer risk assessment for the other members of the patient’s family. So we decided to take this to its furthest step to see if we could figure out the mutations that predispose a particular family.”

The presence of the BRCA gene mutations has calculable genetic risk factors for breast cancer. About 1 in 400 individuals in the general population may test positive for a mutation in the BRCA1 and BRCA2 genes. Mutation in BRCA1 and BRCA2 are responsible for approximately 5 to 10 percent of all breast cancers, and for approximately 50 percent of all hereditary breast cancers. Additionally, 8 percent of all women in the general population will develop breast cancer by age 70; whereas 66 percent of BRCA positive women will manifest the disease. Approximately 1 percent of the general population will develop ovarian cancer by age 70; but 31 percent of BRCA positive women will, by age 70, develop ovarian cancer.

Additionally, certain populations are more likely to carry mutations of the BRCA genes. Individuals with Ashkenazi Jewish ancestry have a significantly higher risk than the general population – about 1 in 40. BRCA gene mutations are also more common in Norwegian, Dutch, and Icelandic populations.

Research conducted by faculty at The Pancreas Center published in 2014 found that approximately 10 percent of pancreatic cancers seen in The Pancreas Center are associated with breast and ovarian cancer syndromes caused by BRCA1 and BRCA2 mutations. Other researchers have found the link between pancreatic cancer and BRCA2 mutations to be as high as 19 percent.

Why Genetic Testing?

“The patient who is identified as BRCA positive when diagnosed with pancreatic cancer should be screened for ovarian and breast cancer and vice versa,” says Dr. Chabot. “We need to manage the patient’s care, but also advise the patient’s family members and encourage them to be evaluated. If a family member is identified with a BRCA1 and/or BRCA2 gene mutation, there are implications for treatment. For example, early screening for pancreatic cancer may be recommended when certain risk factors, particularly positive genetic associations, are present. Early screening can lead to early diagnosis of pancreatic cancer at a stage when it is most treatable. If a specific gene is identified, it is generally accepted that screening with an MRI or endoscopic ultrasound should begin at an age of 10 years younger than the youngest family member affected.”

In addition, pancreatic tumors have increased susceptibility to certain chemotherapies. “Identifying someone with pancreatic cancer with these gene mutations may guide the type of chemotherapy recommended,” adds Dr. Chabot. “Our patients have had improved responses to individually tailored therapy regimens based on genetic testing.”

Fay Kastrinos, MD, a gastroenterologist in the Division of Digestive and Liver Diseases, NewYork-Presbyterian/Columbia, works with families who are at a high risk for almost all of the inherited gastrointestinal cancers. “Pancreatic cancer can be associated with multiple familial cancer syndromes. The connection and risk of pancreatic cancer may be with cancer syndromes involving breast, ovarian, and colorectal cancers, as well as melanoma. The connections can be very broad,” Dr. Kastrinos says. “And now, because genetic testing has expanded to where we can simultaneously test multiple genes associated with cancer, we have more information beyond family history alone to define at-risk families.”

The advances in gene discovery and the increase in speed in performing genetic testing has lowered costs and broadened the number and variety of genes being examined. It has, furthermore, created an ever-deepening pool of information and exciting developments in understanding the genetic predisposition to multiple malignancies.

“A lot of information is continually becoming available,” notes Dr. Kastrinos, underscoring how quickly technology is changing the knowledge related to the inherited predisposition of certain cancers. “What is important to achieve in a high-risk cancer genetics and prevention program is identifying which genes are important to consider testing for, interpreting the results of testing, and the associated risks of cancer, and concluding which results are clinically actionable and meaningful, where options for screening for cancer prevention can be considered. How are we going to translate this better understanding into what we recommend for patients who are diagnosed with cancer, but also extend this to the at-risk family members, many of whom are yet to be affected by cancer? While these questions seem to be better addressed for breast and colorectal cancer, it is intensely poignant for the pancreatic cancer patient identified to carry an inherited cancer gene, such as BRCA, or a family member who is predisposed for it.”

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Dr. Kastrinos stresses the necessity for a comprehensive multidisciplinary approach to taking care of patients and families with these gene mutations. It involves a team of oncologists, surgeons, pathologists, radiologists, gastroenterologists, and genetic counselors, and the approach to each patient and family is personalized. “In our program, we hone in on each individual and the details related to their personal cancer and also those in his or her family,” she says. “Cascade testing is performed to expand genetic risk assessment to family members and gives us the ability to prevent cancer before it develops.” Each time there is a new development, Dr. Kastrinos and her colleagues bring any actionable advances to the families.

The developments in early treatment and targeted therapies for colorectal cancers are far clearer than for pancreatic cancer. For pancreatic cancer the picture is still complex. The options for surgery are greatly reduced, and there are few opportunities for examining the specific tumor, as in colon or breast surgeries. Early detection remains the best defense.

“For example,” says Dr. Kastrinos, “in colorectal cancer we can actually look at the tumor and do DNA testing, and different stains of the tumor can give us some insight as to what’s happening on a genetic basis. The results from tumor studies can guide our decision-making related to genetic testing. With pancreatic cancer we have to rely more heavily on the family history and the presence, or absence of, multiple cancers. When looking at the family history of those who come in with pancreatic cancer, we have been surprised to find previously unseen connections — pancreatic cancer related to breast-ovarian cancer syndrome, melanoma, or related to a colon cancer familial syndrome. Not every physician is going to know all of the different clinical criteria associated with familial cancer syndromes that will drive when genetic testing should be considered."

The optimum step for the family with a history of pancreatic cancer is a referral for a genetics evaluation. “These families need specialized attention, which includes genetic referral and evaluation,” advises Dr. Kastrinos. “Here at Columbia, our families receive counseling pre-testing and post-testing, which is very important for appropriate and timely follow-up. The evaluation is comprehensive from whom should have genetic testing, how do we interpret the results, and how do the results guide the care and clinical management of our patients and families.”

Both Drs. Chabot and Kastrinos are extremely sensitive to the issues involved in genetic testing for the patient and their family members. “We generally recommend to the patient that they deal with the cancer that they’re facing first,” says Dr. Chabot. “After they recover, we then focus on prevention for the other organs that could potentially be involved, as well as testing of family members.”

Dr. Chabot and Kastrinos are in regular communication with their breast cancer colleagues at NewYork-Presbyterian/Columbia. Among them is Katherine D. Crew, MD, MS, a medical oncologist in the Division of Hematology/Oncology at NewYork-Presbyterian/Columbia.

“In our clinical breast cancer prevention program, we counsel women who may be at high risk for developing breast cancer,” says Dr. Crew. “Those who test positive for a BRCA mutation will be followed in our high-risk prevention program so that we can counsel them on the potential for risk-reducing surgery, medical management, and intensive screening. In this program it becomes much more about comprehensive care working together with the geneticist, the surgeon, our social workers, and our psychiatrists. This is not only for the patient, but also for their family members as well in terms of discussing options that are available for them to help manage their cancer risk.”

Dr. Crew points out that it is much more difficult to elicit a family history for abdominal, ovarian, and pancreatic cancer. “People can usually remember if a woman had a mastectomy or some sort of breast surgery, which we can assume could have been breast cancer. But for cancers that present in the abdomen with very late stage disease, you can’t pinpoint where that cancer started and whether it was in the ovaries, pancreas, stomach, or elsewhere in the body,” says Dr. Crew. “In light of what we now know for both men and women who carry the BRCA mutations and the link to pancreatic cancer prompts us to refer patients to Dr. Chabot’s Pancreas Center and Fay Kastrinos’ program.”

“We see hundreds of people from this region who are carrying BRCA gene mutations, and we employ a truly interdisciplinary team, which personalizes and creates targeted treatment or prevention if possible,” says Dr. Chabot. “As we discover these unforeseen connections, such as the link among breast, ovarian, and pancreatic cancers, we can continue to develop and offer effective clinical protocols and remain hopeful.”

Reference Article

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“But these techniques have changed, whereby we are able to give medications to stimulate stem cell production then collect stem cells from the peripheral blood stream,” explains Dr. Phillips. “That is why we sometimes use the terms ‘bone marrow’ and ‘stem cells’ interchangeably. Really, it’s a stem cell transplant. There are studies now showing that stem cells collected from the peripheral blood stream have similar outcomes, but less toxicity, than those harvested from bone marrow.

“Supportive care for transplant patients has also greatly improved,” continues Dr. Phillips. “We are able to support patients and prevent infections, particularly viral infections, with new, promising therapies. We are also making strides on graft-versus-host disease. Even with a perfectly matched donor, patients typically take anti-rejection medication after their transplant. We can further minimize the risks of graft-versus-host disease by changing the conditioning transplant regimen and depleting grafts of T-cells. In the future, transplants will become increasingly safe and tolerable for the patient. This is particularly meaningful for patients who have aggressive hematologic malignancies as transplant may be the only remaining treatment option if they fail other options.”

The work of treating hematological malignancies remains a meticulous process with many dilemmas yet to be untangled. But the progress is significant. “We can face hematologic malignancies with a great deal of optimism,” says Dr. van Besien. “There is incredible opportunity for lifesaving treatments, with greatly reduced side effects and much wider applicability than 20 years ago. There is probably a huge number of patients who, 10 years ago, would have died of leukemia without ever being offered the possibility of a bone marrow transplant. Now they have at least a 50 percent chance of cure. That’s quite noteworthy. We are now at the point where we can offer transplants to basically anyone—regardless of age and background—who walks through our doors.”

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Research at a Glance

New Technique Prevents Lymphedema in Breast Cancer
Early data from a NewYork-Presbyterian/Columbia pilot study suggests that an innovative microsurgery technique helps prevent lymphedema in breast cancer patients. The study of the lymphatic microsurgical preventive healing approach, or LYMPHA, was the first conducted outside of the University of Genoa in Italy, where the technique was developed. LYMPHA was designed to help prevent lymphedema by creating a bypass to restore lymphatic flow by connecting lymph vessels to a branch of the axillary vein, a pathway normally severed by node removal. This preventative bypass is performed immediately after lymph node removal so that the normal lymphatic flow is maintained.

In the study, 37 women considered to be at the highest risk for developing lymphedema underwent LYMPHA. Nearly 90 percent who successfully underwent the study did not develop lymphedema. In the control group of patients who did not undergo the procedure, 40 percent have experienced lymphedema requiring ongoing treatment.

“These results are extremely encouraging,” says Sheldon M. Feldman, MD, Chief of the Division of Breast Surgery at NewYork-Presbyterian/Columbia and the study’s principal investigator. “While LYMPHA is still a relatively new procedure, we found it to be extremely effective in preventing lymphedema in this pilot study.”

Reference Article

Promising Treatment for Mantle Cell Lymphoma
A combination therapy lacking many of the debilitating effects of traditional cancer treatment effectively manages mantle cell lymphoma (MCL), shrinking the aggressive and incurable malignancy and inducing remissions in the vast majority of patients, according to new research from Weill Cornell Medicine.

The findings demonstrate that the pill lenalidomide, taken in combination with the antibody rituximab, provides an effective alternative to chemotherapy, the traditional treatment for MCL. More than 90 percent of patients in the small efficacy trial responded to the therapy, with their cancer shrinking by more than half, and two-thirds of that group had no evidence of detectable tumor growth after treatment. When the investigators examined longer-term outcomes, they found that the results held steady for 85 percent of patients after two years. Patients were generally able to comfortably go about their daily lives, reporting a high quality of life throughout treatment, according to validated measures.

“We were able to achieve a very high quality and durable response rate without needing to use chemotherapy,” says lead author Jia Ruan, MD, a member of the Sandra and Edward Meyer Cancer Center and an oncologist at NewYork-Presbyterian/Weill Cornell. “It’s very meaningful for the patients who have always been told that their disease is without a cure.”

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